CHAPTER XIII-A

CHRONIC CARDIAC VALVULAR DISEASE

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Introduction

Chronic endocarditis is a rather archaic general designation It has been used synonymously for chronic deforming valvulitis It would however, include every type of chronic endocardial disease that results from infarction and degenerative changes as well as that following infection of the endocardium in general and not alone that covering the valves Chronic cardiac valvular disease is the preferable term but chronic valvular endocarditis or deforming or rheumatic valvulitis may be applied to almost every case of rheumatic heart disease Rheumatic fever is by far the most common etiological factor There are only rare cases with other types of acute and subacute bacterial valvulitis that survive and present scarred defective valves Syphilis very frequently produces an aortitis that involves the aortic root and ring and results in a secondary valvular defect that is accompanied sometimes by chronic fibrosis which spreads from the broadened commissures to the edges of the cusps

Chronic cardiac valvular disease connotes heart disease in which one or more valve leaflets, sails or cusps have been thickened and deformed by fibrous or scar tissue Such scars have resulted in incompetency that is inability of the valve to close tightly or to open completely or to do both Enlargement of the heart, in part due to dilatation and in part to myocardial hypertrophy, is demonstrable eventually in almost all patients with deformities of one or more valves The diagnosis heart disease denotes that reliable signs are demonstrable, which indicate the presence of damage which sooner or later will lead to heart failure myocardial or coronary insufficiency The inevitable failure often may be postponed many years by careful management, but the serious potentialities of valvular lesions should be recognized

Early recognition and accurate interpretation of defective valvular functioning by a discreet and tactful physician will add many years of productivity and comfort to the life of the patient Good practical psychology must be exercised

in the outlining of the necessarily limited pattern of life for the cardiac invalid The dangers and possible complications must be kept in mind but great care must be taken to avoid alarming the patient and causing unnecessary worry Reas surance is justifiable, and the citation of instances of well known individuals who in spite of valvular lesions enjoyed happy complete and successful lives usually is inspiring to the patient with valvular heart disease

INCIDENCE

The incidence of valvular deformity varies considerably according to geo graphical or climatic factors, the type of the physician s clientele and the general average age of his patients Statistical data on incidences are therefore, of little diagnostic or prognostic significance In general however when the evidence is insufficient a diagnosis of a commonly occurring lesion is far more likely to be correct than is a diagnosis of a rare condition Chronic cardiac valvular diseases are found chiefly in children adolescents and young adults fairly often in the 40 to 50 age group occasionally in those of older age and rarely in the aged

At the John Sealy Hospital the general teaching institution of the University of Texas Medical Branch the incidence of rheumatic heart disease is consider ably lower while that of syphilitic aortic disease is higher than in northern hos pitals During the past two decades 1920 to 1939 there have been 6 987 cases of all types of heart disease among 19 802 medical patients out of 104 392 total admissions Of the 6 987 cardiac patients 5 684 or 81 per cent were diagnosed as having chronic myocardial disease of primary hypertensive or coronary arterio sclerotic origin of the other 1 239 or 18 5 per cent 814 or 11 5 per cent pre sented signs of syphilitic aortitis with aortic regurgitation while rheumatic valvulitis was diagnosed in 371 or 5 3 per cent and congenital lesions in 108 or 1 4 per cent These clinical figures when compared with those reported by Dr Henry A Christian from the Peter Bent Brigham Hospital suggest that rheumatic valvulitis is five to six times more common in the patients of the Brigham in Boston than in those of the Sealy in Galveston On the other hand syphilitic aortitis is two and a half to three times more common and congenital lesions three times as frequent in the population of the Sealy as in that of the Brigham The Brigham however admits no children under the age of twelve years

Pathological Statistics

Rheumatic fever is a chief etiological factor in the great majority of cases of chronic cardiac valvular disease It will be therefore advantageous to sum marize some of the recent surveys of the incidence of the different types of

Garvin[1] of Cleveland City Hospital reported the 1930–1940 decade series from 6 548 autopsies In his selected 119 cases that had died primarily of rheumatic heart disease the mitral valve was involved in 116 the aortic in 86 the tricuspid in 23 and the pulmonic in 5 The Cleveland series showed that 43 or 36 per cent of the 119 cases had involvement of the tricuspid valve with 10 9 per cent of these advanced to the point of definite tricuspid stenosis Coombs had found that 34 per cent of his cases of chronic valvulitis presented tricuspid involvement, but only 14 per cent showed tricuspid stenosis Dressler and Fischer in 1929 reported 30 cases of tricuspid disease in only 5 of which there was true stenosis Most of the 250 cases compiled by Zeisler in 1933 had slight degrees of stenosis

Von Glahn in 192, found the tricuspid valve acutely involved in 19 and chronically involved in 26 of a series of 109 autopsy cases which is a total of 45 or 41 per cent Cabot in 19 6 found among 4 000 autopsies at the Massachusetts General Hospital between 1896 and 1919 that 33 of 220 cases of valvulitis 13 per cent, presented tricuspid stenosis Thayer in 1925 reported 44 per cent tricuspid disease in the Johns Hopkins autopsy series Libman in 1923 found some involvement of the tricuspid in 665 per cent of cases of acute rheumatic endocarditis Tricuspid involvement therefore is not uncommon Futcher in 1911 found only 14 cases of tricuspid stenosis out of 195 and 4 more reported incidences were compiled by Clements Isolated involvement of the tricuspid, however may be numbered at 18 cases on record

It is important to realize the frequency of combined lesions and the relative rarity of single lesions or lesions in a single valve The mitral valve is the one that is involved alone most often in about 25 per cent of the cases Practically all valvulitis in all other valves is associated with mitral disease It is surprising that the aortic valve is involved alone so rarely only 4 per cent of all rheumatic cases at the most Trivalvular lesions were found in 6 cases while all 4 valves were affected in 11 of the 53 cases of rheumatic valvulitis summarized in Table I Krumbhaar found quadrivalvular involvement in 4 cases of his 437 cases of endocarditis Four of McGuire and McNamara s[110] cases of pulmonary insufficiency showed all four valves involved

Acquired pulmonic valvular lesions are the most infrequent of chronic valvular disease particularly so those of the organic acquired type Hirschfelder found only 3 cases of acquired pulmonic insufficiency in 24 000 autopsies at the Johns Hopkins Hospital Rehfisch found 9 instances of acquired pulmonic insufficiency in 3 000 autopsy proven cases of heart disease Pitt and Salter in 1913 found 24 cases of acquired pulmonic insufficiency in 1 600 autopsies at Guy s Hospital From the literature with their own cases they had 109 cases of which half were acute lesions another quarter were relative lesion and 13 showed multi

valvular involvement only 14 of these definitely showed organic pulmonic stenosis Krumbhaar in 1928 found the pulmonic valve affected 14 times in 437 cases of endocarditis The author of this chapter found 5 cases of chronic healed rheumatic pulmonic valvulitis only one of which showed stenosis and none as sole lesions, in 4 776 autopsied cases of heart disease at Charity Hospital, New Orleans Three additional cases of pulmonic incompetency have been seen in 1,500 autopsied cases at the John Sealy Hospital in Galveston

Vellguth[10] in an exhaustive survey of the German literature up to 1931 concluded that pulmonic lesions were very rare He cited Finkelstein s 4 cases of pulmonic insufficiency in 435 autopsies and Schultze s 4 cases of pulmonic insufficiency in 909 cases McGuire and McNamara found 14 proven cases of pulmonic insufficiency in the files of the Cincinnati General Hospital Nine of these cases were reported in detail and in the 4 of rheumatic etiology all 4 valves were affected

These brief statistical comparisons serve only to emphasize the considerable variation in the frequency of occurrence of the various types of heart disease in the north and in the south sections of the United States The incidence of the types of heart disease from private practice are known to vary sharply from those of teaching institutions Statistical data thus can be used at best only as a rough guide in diagnosis and primarily to acquaint the examiner with the rarity of certain conditions The wise physician will hesitate to make an unusual diagnosis unless he has elicited definite criteria of a rare condition

The fact that many a patient s heart often seemingly compensates adequately for extensive valvular damage and often supports strenuous exertion for several years has inspired a rather unjustifiably casual attitude toward chronic cardiac valvular diseases The preponderant emphasis that has been placed on the condition of the heart muscle unfortunately has put out of fashion for a time the careful physical diagnosis and exploration of the precordium and the detailed study of the valvular sounds inadvertently has been somewhat neglected

The art of diagnosis of chronic cardiac valvular disease has been revived because the conditions are recognized as important not only in academic work but also in practice At the same time interest has been aroused in the more careful physical examination Valvular dysfunction in itself at times seemingly may lead directly to myocardial insufficiency It probably contributes significantly to the failure of the heart whose heart muscle was extensively damaged at the time of the acute valvulitis

Chronic cardiac valvular diseases well may be emphasized and accorded more attention in routine preschool and grade school examinations The early recognition and proper respect for the presence of a valve lesion in a patient s heart by a good doctor well may be a great benefaction to the patient Often good sane

advice may contribute to postponing or preventing early and complete failure of the heart It must be remembered that occasionally the sign of what appears to be mitral stenosis in an acute rheumatic fever case disappears Directly after an acute attack no murmurs may be heard yet these same signs may appear years later

The general internist and also the modern practitioner is expected to know the pathological physiology the diagnosis and the prognosis of the common valvular disease The subject is important even though there is little in the way of specific treatment other than management that can be prescribed for those patient having signs of fibrosed deformed heart valves Good general care judicious encouragement and restrictions are most important to those so afflicted The recognized danger that irreparable damage may be done by insidious disease to such vital structures as heart valves should emphasize the need for studies on the nature and methods of control and the natural history of the causative factors and the pathological processes

Specific Origins and Genesis of Valvular Defects

Rheumatic fever is the chief and almost the sole cause of chronic cardiac valvular disease It may occur as acute migratory arthritis chorea scarlatina tonsillitis erythema nodosum or growing pains A characteristic acute clinical picture has failed to develop or has gone unrecognized in half of the cases or more of rheumatic valvular disease in the South No one of the many incriminated organisms has been generally accepted as the etiological agent in rheumatic fever in spite of a tremendous amount of careful bacteriological work and the isolation of various supposedly specific anhemolytic streptococci by Poynton and Paine[1] Coombs Clawson Coburn[3] and others down to Swift and Brown s[4] pleuropneumonia like microorganism

The specific rheumatic fever lesion the Aschoff body is such that a virus[5] may be considered to be the primary causative agent but no specific form as yet has been isolated The beta hemolytic streptococcal upper respiratory tract infections certainly play a most important role and seriously aggravate rheumatic fever manifestations Much has yet to be learned concerning bacterial symbiosis Streptococci may play a significant part along with a true but yet unidentified virus Streptococci are considered by some investigators to be secondary invaders in rheumatic fever

It would seem best at this time to postpone the acceptance of any organism as the etiological agent of acute rheumatic fever and wait for further time tested proof establishing the part played by a specific streptococcus or a specific virus There has been much recent work done on the epidemiology the protean early

manifestations and the natural history of rheumatic fever The observations that have been made even though incomplete, will help to guide us in the management of cases of acute rheumatic fever There is some hope of preventing curing or of minimizing the subsequent damaging scarring and fibrosis of the valves

The prophylactic use of sulfanilamide in doses of 1 to 2 grams per day in known rheumatic children from October to June has proved successful by Coburn and Moore[6] and by Thomas and her associates The use of salicylates in the prevention of recurrences previously was unsuccessful probably because of inadequate dosage Coburn and Moore have had success in prophylaxis with 4 to 6 gm (gr 60 to 90) doses of salicylates per day Salicylates have been advocated as good treatment for the patient who shows no idiosyncrasy to the drug

Syphilis the most common cause of aortic regurgitation in the South[8], is of known etiology and pathogenesis Even though it does not produce a primary valvulitis[9] there are secondary changes and differential diagnostic facts which warrant its consideration here[1 11] The evolution and peculiar nature of the aortitis for which there is specific therapy, is well recognized by many physicians but is rather neglected by those with patients all of high moral character Serological tests are available and are used generally to test for the presence and the persistence of the infection

The activities of the United States Public Health Service against syphilis and particularly the insistence on the necessity for continued early treatment by specific drugs should accomplish much in the prevention of syphilitic aortitis Methods for the prevention of aortitis and of aortic regurgitation as well as other types of late manifestations of syphilis deserves extended further study More might be expected from the antisyphilis campaign than from the antirheumatic fever prevention campaign because we know so much more about the treatment of syphilis and have more specific remedies for it Early continuous and vigorous treatment of the infection is more successful than massive therapy later

Congenital valvulitis in the foetus as the result of an active infectious disease in the mother occurs rarely[10] Usually this should be prevented by active treatment of the mother during pregnancy Congenital anomalies of the valves fortunately also are quite rare The causal and formal genesis of hypoplastic and aplastic processes in the embryo are unknown and therefore no steps to be taken in their prevention can be set forth[11]

Acute pyogenic valvulitis complicating general infections occasionally may be survived only to yield or produce cardiac valvular disease Subacute bacterial endocarditis due to secondary invasion of alpha streptococci may heal occasionally[1 4 1] In the presulfonamide days fulminating bacterial valvulitis practically always was so promptly and uniformly fatal that valvular disease of such etiology

was practically unknown Sulfonamide survivals with valvular scars may be expected in somewhat increasing number The ulcerated valve may heal, but usually there is a resulting considerable destruction and defective function Better care is now given to patients with infectious diseases and the administration of high vitamin diets accompanied by high vitamin concentrates may decrease the number of cases of valvulitis and of myocardial damage

Atheromatous and *calcareous* diseases in the valve rings and leaflets is a chronic degenerative process of unknown etiology (Monckeberg 1904 [6]) These abnormal metabolic changes usually take place in the tissues damaged by previous inflammatory disease, particularly rheumatic fever[17] Pure atheromatous valvular disease is primarily degenerative and is very rare indeed It occurs only in the prematurely aged individuals who have serious disturbances of fat and calcium metabolism

General Etiology and Pathology of Valvular Disease

Rheumatic valvulitis may begin insidiously during an unrecognized infection with the rheumatic virus The manifestations of rheumatic fever are quite variable The acute, inflammatory migratory arthritis is a rare clinical picture in the South though it does occur Chorea likewise is most uncommon However tonsillitis is quite common less common are pneumonitis pleuritis erythema nodosum and rheumatoid arthritis following any of which pericarditis and rheumatic valvulitis may occur During any obscure febrile condition of childhood and early adolescence rheumatic fever should be suspected and involvement of the heart looked for Pain over the heart, weakness and breathlessness suggest carditis This is particularly so if the fever and exudative lesions respond as they usually do within 48 hours to adequate salicylate dosage and tachycardia with or without a systolic or a presystolic murmur gallop rhythm or a pericardial friction rub persists[18] The presence of a leucocytosis and increased blood sedimentation rate electrocardiographic signs as atrial ectopic beats or A V conduction disturbances along with roentgenographic evidence of cardiac enlargement are confirmatory signs of rheumatic carditis and valvulitis[18 19]

Most of the acute rheumatic changes in the heart are allergic or immune or toxic reactions The various specific factors and diverse physical chemical and pathological processes involved in localizing inflammatory reactions are unknown Exudation with edema and infiltration with various types of cellular elements and later with angioblasts and fibroblasts develop more or less rapidly The Aschoff body and minimal valvular endocardial erosion are characteristic [0 1] Only very occasionally are the etiological agents in the form of microorganisms present in or on the valvular tissues Rheumatic lesions usually are bacteria free At least

bacteria are demonstrable post mortem only in very rare cases[10] Occasional cases with destructive pyogenic valvulitis may be expected to survive, especially under sulfonamide therapy and present chronic valvular lesions

Years usually elapse between the acute disease and the presentation of signs of valvular disease The healing of a valvulitis leaves a scar, which is of significance especially if there has been fusion of the edges of the cusps The healing scar contracts and may constrict and narrow an orifice or prevent valvular closure It may produce only very little deformity and interfere but slightly with the valve function

The significance of the presence of more or less vascularized fibroblastic or fibrous tissue in the leaflets lies also in the fact that it predisposes the valve to secondary subacute bacterial endocarditis In more extensively fibrosed valves the deformity is very disturbing to function adds considerable strain and stimulates the development of pathological hypertrophy of the heart and eventually contributes to dilatation of the heart

The grade and rate of the evolution of the chronic valvulitis certainly is not the same in all patients nor the same in all valves of the same patient Probably there are several factors to determine this but most of these are unknown Rheumatic fever involves the valves of the left side of the heart more regularly than those of the right heart or better sooner or more markedly No completely satisfactory explanation for this has been given The possibly contributing effects of higher blood pressure and more vascularization as predisposing factors have been mentioned The mitral valve alone may be damaged occasionally When there is aortic or tricuspid valvular disease the mitral valve usually is affected also Rheumatic pulmonary valvulitis is most rare Mitral stenosis and slight insufficiency or aortic incompetency with slight obstruction are encountered most commonly They are associated in a third of the cases High grade mitral disease will show associated tricuspid disease in a third of the cases usually also with aortic valvulitis The aortic and more especially, the tricuspid valves rarely are involved alone

Aortic valvular dysfunction may decrease the blood flow through the coronary arteries High grade mitral disease by virtue of the fact that the left ventricular output into the aorta is reduced has a similar effect In addition to this the chronically engorged left atrium may cause pressure atrophy about the circumflex branch of the left coronary artery and compress it and thus interfere with the oxygenation and the nutrition of the myocardium of the left ventricle By retraction of the reflecting cusps and by decreasing the diastolic blood pressure level aortic regurgitation contributes to coronary vascular insufficiency Narrowing of the coronary orifices by the aortitis adds further to the embarrassment of the coronary flow

Rheumatic Fever Valvulitis The Pathological Anatomy

A knowledge of the histological changes in acute and subacute valvulitis is conducive to a clearer understanding of the healed deformed valves The specific Aschoff body rarely develops typically in the valves as it does in other cardio vascular tissues, especially in the heart muscle and around arteries [0] The characteristic lesion develops about endothelial cells with central single or multiple nuclei and fibroblasts [1] The acute lesion with much necrosing tissue calls forth polymorphonuclear cells while in subacute states lymphocytic and plasma cells are found in the Aschoff body In acute rheumatic valvulitis there is a swelling of the valve cusps and a fraying of the collagen fibrils of the supporting substance by edema and cellular infiltration according to Clawson Bell and Hartzell [3]

The exudative process promptly becomes complicated Wandering cells some of which are giant cells similar to those of the Aschoff body are scattered through the loose tissue and histiocytes are polarized to form a palisade of cells with long axis at right angles to the surface localized within the substance of the valve particularly along the line of closure The surface endothelium probably is secondarily but promptly eroded from within becomes necrotic and denudation occurs in the areas of contact according to the careful work of Swift [4] Deeper ulceration usually does not follow

The damaged valve leaflets at the points devoid of endothelium collect platelets and fibrin this becomes granular and builds up minute to pinhead size vegetations which protrude from the surface of the leaflet along the line of closure [5] The inflammatory exudate usually slowly extends through the swollen collagenous tissue often causing fusion of the free borders of the mitral valve leaflets extending up to the ring of attachment and down the chorda tendineae later to be organized to heal and to contract

At the base of the vegetation in the substantia of the leaflets there occurs an infiltration of mononuclear cells with basophilic cytoplasm sometimes arranged in palisades Occasionally polymorphonuclear leucocytes and eosinophiles are present The endothelium usually regenerates over the vegetation and forms a smooth clean surface producing a slight elevation with semitranslucent bead like verrucae [4]

At first the valve rings may be dilated the valves may not close completely and valvular insufficiency may be the result Sometimes no murmurs of incompetency appear in the patients who later present signs of obstruction at the mitral orifice On the other hand the ventricle may be inordinately dilated and the auriculo ventricular ring may regain its normal status This may give rise to a pseudo obstruction to the flow into the ventricle A confusing presystolic murmur may be heard during the acute disease disappear completely later and still be

absent after a decade The fusion of the closely approximated, denuded valve borders ordinarily progresses slowly It usually takes many months for the edges of the mitral valve to be brought together sufficiently to produce the more significant and characteristic anatomical deformity When this is accomplished, there is obstruction enough to the diastolic inflow into the left ventricle to produce the diagnostic rumble heard at the apex

Fibroblasts and angioblasts of the valve surface grow into the area of fusion and into the vegetation The small blood vessels increase according to Wearn and Moritz[3] There is also proliferative infiltration as the interstitial inflammation progresses Usually the process extends down into the chordae tendineae As the lesions become older lymphocytes and plasma cells are attracted and occasionally Aschoff bodies develop Verrucae usually become greyish yellow, opalescent and form ridges along the line of closure of the leaflets, most commonly in the mitral and in the aortic valve fairly frequently in the tricuspid but rarely in the pulmonic valve[7]

In spite of the unexplained great immunity of the pulmonic cusps to rheumatic valvulitis Kugel and Epstein presented as evidences of each attack of rheumatic fever a layer of scar tissue in the pulmonary conus at the root of the pulmonary artery Involvement of the aorta and coronary arteries by the rheumatic process adds further complications to the aortic valvular defect[30] Rheumatic aortitis and coronary arteritis may contribute to coronary and myocardial insufficiency Pericarditis often develops to complete the picture of rheumatic pancarditis Pulmonary and pleural lesions may inaugurate rheumatic fever in childhood, and the cardiovascular exacerbation may follow rheumatic pleuritis or pneumonitis[31] Rheumatic peritonitis is a rarity but does occur

Evolution of Rheumatic Lesions of the Heart Valves

Proliferative connective tissue infiltration of the damaged valves progresses very slowly after the exudative stage but continues and sometimes increases with each exacerbation of rheumatic fever Fusion of the mitral valve leaflets and the free borders of aortic cusps at the commissures progresses slowly An early presystolic murmur has been recorded and found to disappear by St Lawrence[7] The verrucae are replaced by fibrous tissue producing a diaphragm of scar tissue much more often in the mitral than in the aortic ring Exacerbations add further insult to injuries previously sustained The scar tissue thickens and stiffens and the valves and the chordae tendineae shorten after a few years The leaflets and cusps become taut do not open or close completely and thus obstruct the flow of blood through them or fail to hold the projected stream and thereby produce so called stenosis or regurgitation

The mitral valve most typically becomes a fibrous diaphragm with narrowed fish mouth or button hole orifices drawn down funnel shaped as a result of shortening of the chordae tendineae If fusion has not been so complete at the edges of the leaflets as usually is the case in the tricuspid valve lesions contraction of the scar tissue in the chordae tendineae may be more marked and predominately insufficiency of the mitral or tricuspid valve results

In the aortic valve infiltration of the cusps shortens the free edges and then they fail to make complete contact on closure Fusion at the aortic commissures is less conspicuous but it does occur and not infrequently stenosis develops and later the scarred cusps become calcified Aortic insufficiency or incompetency is most common and free regurgitation of blood back into the left ventricle takes place during diastole

As the interstitial fibrosis increases thickening of the upper part of the cusp produces later a rolling curling and retraction of the border as the most common anatomical deformity Sometimes the stiffened cusps maintain a position such that the functioning aortic orifice is roughly triangular The aortic cusps less frequently are fused extensively to form a conical diaphragm and only occasionally are approximated and calcified to the point of producing significant obstruction at the aortic orifice

Processes similar to those described as occurring in the mitral and aortic valve leaflets may develop occasionally in the tricuspid valve and most rarely in the pulmonic valve The tricuspid valve is so filmy and so divided that fusion only *rarely takes place and high grade tricuspid stenosis is uncommon* Rheumatic involvement of the pulmonic valve cusps is rare but relative incompetency develops in some patients who also have high grade mitral stenosis The unusual as well as the usual clinical pictures of valvular disease and dysfunction are recognized by astute clinicians

Chronicity and Recurrences in the Course of Rheumatic Valvulitis

Rheumatic fever is not strictly an acute disease recrudescences and exacerbations are the rule There is a definitely seasonal tendency paralleling the course of streptococcic infections Sometimes long periods of quiescence mark the presence of smoldering foci of infection as expressed in the axiom once rheumatic always rheumatic Chavez[33] has pointed out that in Mexico rheumatic fever usually is a continuous chronic granulomatous disease like tuberculosis In the northern U S A and in England intermittent activity is the rule throughout adolescence Each flare up of the disease process adds more serious and widespread insult to the injuries and damage that have been developing slowly

Acute and often fatal myocardial insufficiency is precipitated usually by recur

rence of activity Rheumatic fever lesions are not confined to the valvular tissues but pancarditis is common with Aschoff nodules developing concomitantly in the endocardium of the left atrium in the perivascular connective tissues in interstitial tissues about the coronary arteries, in the supporting muscle bundles in the myocardium and in the adventitia of the aorta which is involved simultaneously by the same virus process

Late in life the fibrous tissue becomes hyalinized and acellular The minute capillaries become constricted by scar tissue except at the base Calcium deposition takes place in the scar tissue of the aortic root and valve[34, 3] and in the fibrosed mitral valve funnel[6] as well as in other parts in the myocardium and in the pericardium Calcium may again erode the endothelium and collect some fibrin strands

Evolution of Syphilitic Aortitis and Aortic Valvular Insufficiency

Syphilis produces very slowly as a rule a disease process at the root of the aorta and in the aortic ring[1, 11, 3, 35] There is an infiltration about the vasa vasorum with plasma cells and lymphocytes and intimal proliferation and obliteration of the nutrient vessels to the aortic and other arterial walls The intima and media are thickened by granulation like tissue and a rich cellular mobilization of histiocytes lymphocytes and plasmocytes Warthin[3] and others demonstrated the treponema pallidum in the infiltrated areas in the aortic wall Some areas of heavy cellular infiltration may have central necrosis simulating miliary gummas often with a few multinucleated foreign body giant cells

The aortic wall is weakened by rupture of the elastic lamellae and replacement of the smooth muscle cells by collagen The blood pressure dilates the aorta the infarcted wall of which is thinned as a result of obstruction of the vasa vasorum and the consequent degeneration of the elastica and its replacement by fibroblasts in these places with a resulting thinning as well as scarring of the media[3, 4, 41]

In rare instances a serpigenous syphilitic ulcer of the aortic intima has involved an aortic cusp[4] In general the intima in syphilitic aortitis is thickened by connective tissue proliferation and shows sharply definite pearly white hyaline elevations with flat smooth porcelain like depressions and sharp furrows of variable size and length and of stellate configuration[43] Longitudinal wrinkling or ridging of the intima gives the so called cigarette paper or tree bark appearance

The syphilitic process involves most prominently and significantly the root of the aorta Dilatation of the aortic valve ring separates the anchoring ends of the aortic cusp With the separation of the commissures the edges of the cusps coalesce with the intima of the aorta Separation of the valvular commissures and

the thickening and rolling back of the free borders of the aortic cusps result from chronic mechanical pressure irritation The chronic traumatization of the edges of the cusps by the regurgitant stream causes a spread of fibroblasts out from the commissures with resulting thickening and eversion of the free edges The anterior mitral sail likewise may suffer mechanically induced fibrosis as in the aortic valve leaflets

Syphilitic aortic insufficiency is for the most part a mechanical affair with principally a dilatation of the ring secondarily with the spreading of the com missures and thirdly with sclerosis along the tops of the valves contributing to the dysfunction of the valve[38] This pathological change with the syphilitic process at the root of the aorta produces from the beginning a gradually increas ing aortic ring dilatation and aortic valvular insufficiency This cause of aortic regurgitation must be discussed with chronic cardiac valvular disease even though more properly it should be taken up under the caption of syphilitic aortitis[39] It is a much more serious disease than rheumatic aortitis Syphilis is a chronic inflammatory and degenerative disease and is more prone to produce aortitis and occasionally involvement of the orifice of the coronary arteries [7] than aortic valvulitis Syphilitic aortic regurgitation is found most commonly in adults and middle aged men and usually is considered to be a tertiary process For further discussion of syphilitic disease of the aorta and the aortic cusps see in Chapt XIV–A of this volume

Functional Derangements or Disturbed Cardiodynamics Resulting from the Pathological Changes in the Heart Valves

The functions of the normal filmy valve leaflets cusps or sails of the heart are to direct the blood mass without obstruction or regurgitation Change in the character of the valves as the result of inflammation results in interference with the efficient movement of the blood volume Incomplete closure of an atrio ventricular valve mitral or tricuspid during systole of the ventricle permits an aberrant flow of blood into an atrium as well as pumping a decreased volume through a semilunar valve This adversely effects the movement of the blood mass and thus reduces the effectiveness of ventricular systole Defective appo sition of three borders of the aortic or pulmonic semilunar cusps allows a part of the ventricular output to flow back into the ventricular cavity during diastole This decreases conspicuously the forward propulsion efficiency of the ventricle Only a part of the ejected blood mass then is carried on its normal way by the elasticity of the great vessels

On the other hand fused or deformed mitral and tricuspid valve leaflets are unable to fall back completely against the wall away from the orifices as filmy

valve fails n rmall do Th s results in slight or considerable degrees of obstruction to the flow of blood from the atrium into the ventricle during diastole and thus interferes with the complete filling of the ventricle The greater the fusion of the leaflets and the consequent stenosis of the valve the less adequate is the filling and the more difficult the maintenance of circulatory equilibrium Obstruction in the aortic and pulmonic valve resulting from fusion and thickening and stiffening impedes the flow of blood out of the ventricle into the great vessels This lowers the blood pressure and the pulse pressure and impairs the circulation

Compensatory Processes

Slowly progressive valvular distortions with developing circulatory obstacles and increasing physical burdens are compensated for first by increasingly efficient use of the myocardial strength and later by hypertrophy of the heart muscle The first physiological responses to lengthening or stretching of the muscle fibers are conducive as Starling and Visscher[44] have shown to increased functional capacity and chemical economy of muscle contraction A necessary, yet eventually equivocal response of the damaged heart muscle cells to this stimulus of stress is a tendency to enlargement or hypertrophy[4]

Deform y of some valves increases the amount of blood in some heart chambers and one system while defective action of other valves contributes to engorgement of other cavities and another system Increased heart chamber volumes are necessary to maintain the normal blood flow It is to be remembered that the infection or degeneration which caused the valvulitis, unfortunately often produces changes in the walls of the coronary arteries and in the heart muscle cells These, together with the added strain necessary to maintain an adequate minute volume in the presence of defective valve action will contribute to cardiac enlargement

Some dilatation of the chambers of the heart at times unrecognizable clinically at first increases the functional capacity[1] This dilatation apparently is the primary stimulus to hypertrophy The added work seems to be one of the chief factors and progressive changes take place to maintain the circulatory equilibrium slight changes in blood pressure incident to valvular dysfunction in the greater or lesser circulation may have gradually a significant effect on the muscle nutrition The heart seems to be able to compensate as long as the mechanical handicap increases slowly and the heart muscle integrity and the coronary blood flow are not interfered with too greatly

The extent of the involvement of the myocardium at the time of the initial rheumatic infection may be a determining factor in the maintenance of the circulation Some hearts seem to enlarge faster and to a greater extent than do others with what appear to be similar grades of valvular embarrassment In

some excessive dilatation seems to dominate In others hypertrophy of the myocardium is outstanding In either case the physiopathological process interferes with the blood supply and the oxygenation and consequently disturbs the metabolism and biochemistry of the heart muscle[1] The exposure to sudden physical strain or intercurrent infections and probably other unknown factors intervenes to change the heart muscle and weaken the myocardium

The enlargement of the heart and the individual heart muscle fibers even when this is a very slowly progressive process will lead eventually to functional difficulty as pointed out by Harrison and Ashman[48] and Wearn[49] The hypertrophied heart muscle cell as these investigators concluded and as Christian had surmised is at a disadvantage for oxygenation No concomitant increase in capillaries has been found to accompany myocardial hypertrophy The diffusion of oxygen through the hypertrophied heart muscle fiber obviously is less efficient Relatively inadequate oxygenation or anoxia probably leads to disadvantageous chemical changes in the heart muscle cell and heart failure[0] Sclerosis of the coronary arterial bed with aging in time may contribute likewise to the creation of a vicious circle

The Pathological Physiology of Valvular Diseases as the Bases for Symptoms Signs and Diagnostic Criteria

Mitral Insufficiency

The ominous cardiodynamics of this incompetency depend upon the rate of development and the extent of the defect[1 3 3] Mitral insufficiency is more of a strain on the heart than it generally is considered to be Experimentally MacCallum and McClure[3] and Allan have shown that the burden is particularly heavy only when mitral insufficiency is induced suddenly Chamberlain and Dock s analysis of roentgen cinematographs in mitral disease revealed rapid and conspicuous movements in the dilated atrium and the continuation of this movement into early diastole when mitral regurgitation predominates Regurgitation was demonstrated in animals and in man to continue for $\frac{1}{15}$ to $\frac{1}{10}$ second after the end of systole Barry[8] has shown that hampered by an incompetent mitral valve the functional capacity of the dog s heart is diminished considerably This is very evidently so if the venous inflow is increased and decidedly so in the presence of an anoxemia and secondarily increased peripheral resistance[7]

The changes in chronic organic mitral insufficiency usually are much more gradual than those of a defect induced by rupture or operation and adaptive mechanisms come into play and increase with the increasing load[8] It is appar

ently not a purely mechanical matter of back pressure into the left atrium, thence through the pulmonary circuit and finally to the right heart There is a gradual creation of a systematic blood pressure readjustment An increased diastolic ventricular filling and an increased initial intraventricular tension with a resulting increased ventricular stroke and increased systolic output together with a compensatory peripheral constriction tend to maintain the normal systemic blood pressure levels [9]

The lesser circuit is protected for a time against excessively high pressure by reduced venous return to the right atrium The pulmonary engorgement by acting as an encroachment upon the right heart results in a corresponding reflex reduction in the discharge of the right ventricle Consequently there is a tendency to hold as low as possible the rise in the intrapulmonic pressure With the increased tension and pathological stretching gradual left ventricular hypertrophy takes place Any myocardial damage and insufficiency of any part may jeopardize this delicate compensatory balance mechanism, and the mechanical congestive phenomena may intervene

Failure of the mitral leaflets to close at the end of diastole permits systolic regurgitation of blood through the defect of the valves into the left atrium This gives rise to the blowing apical systolic murmur which is transmitted or propagated in the direction of the blood flow toward the left axilla and produces considerable rise in atrial pressure throughout systole Dilatation of the left atrium by the increased intraatrial pressure is an inevitable result This is reflected back through the pulmonary veins to the pulmonary artery and against the pulmonic valve with accentuation of the pulmonic second sound There is apparently a delicate and effective adjustment or compensatory balance system which in the early stages tends to keep the pulmonary pressure from rising sharply

A slight increase in pulmonary blood pressure apparently is overcome readily, and adequate circulation is maintained by the right ventricle In mitral insufficiency the left atrium is the only chamber that dilates some and hypertrophies but this is not to the extent that is found in mitral stenosis The imbalance of intraatrial pressures may precipitate atrial fibrillation Physical evidences of left atrial enlargement can be gotten only by the expert cardiac roentgen fluoroscopist in the narrowing of the upper retrocardiac clear space in the anterior right 60° oblique position and in the visualization of the displacement of the esophagus filled with thick barium Some compensatory reduction adjustments are made by the right ventricle Nervous impulses or discharges apparently result in reflex peripheral constriction and reflection to the right atrium The right ventricle does not stretch and apparently does not hypertrophy to any significant extent

Cases of extensive traumatism to the mitral valve with suddenly induced re

gurgitation have been described[11] *They have gone on to congestive heart failure and death within a few years without the intervention of any other discoverable aggravating etiological factor* Sudden experimental *mitral insufficiency* was poorly tolerated in the author's series of dogs in which valvular lesions were produced Any success in therapeutic surgical mitral valvulotomy will depend I believe on recognition of these facts Careful slitting of the thickened mitral diaphragm cone might produce simultaneously only a very slight if any complicating regurgitation This in a rare favorable case might allow very little or no added egress or reflux into the atrium while allowing the desired added ingress of blood into the ventricle Failure of the attempted operation may well have been the result of the production of a sudden rather free and apparently overwhelming mitral regurgitation The precipitateness of the change rather than the quantity of the shift of intracardiac pressures and dynamics probably was responsible for the disastrous outcome of several mitral valvotomies

Mitral Stenosis

Mitral stenosis usually is accompanied by insufficiency and the abnormal circulatory dynamics are somewhat similar and tend to modify each other according to the grade of obstruction or incompetency that is present Appreciable obstruction to the blood flow into the left ventricle occurs *when the circumference of the functioning mitral orifice* is reduced to *less than 7 3 cm and the area to less than 450 sq mm* As the *narrowed mitral aperture is constricted further the left ventricular diastolic volume becomes reduced The output from* the left *heart consequently is decreased* and the peripheral blood pressure and pulse pressure fall

Quite contrary to our traditional clinical conceptions mitral stenosis in artificial circulation schemata and the stenosis of the mitral valve produced experimentally seems to add a load that is more easily borne even with very high grade lesions [3], than is the burden of mitral insufficiency The obstruction to the flow of blood from the left atrium into the left ventricle increases quite gradually as a rule Up to a time when the orifice is reduced considerably the left atrium compensates with a greater stroke which with prolonged late diastolic atrial emptying succeeds in filling the left ventricle more or less completely

*The resistance to the discharge of the left atrium increases the left intra*atrial pressure considerably and this is reflected back into the pulmonary circuit This stimulates the right ventricle to increased stroke thus adding further to the *rise of* pressure in the pulmonary system and so slightly sustaining the atrium in its *effort to fill the left ventricle The left atrial myocardium hypertrophies as* does the right ventricular

The impediment to the slow flow of blood from the left atrium to the left ventricle during diastole causes the characteristic, sharply localized apical, low pitched, rumbling, mid diastolic sound that rises in a crescendo to end in a sharp first sound at the apex Greater dilatation of the left atrium and more hyper trophy of the left atrial wall make the visualization of the chamber more strik ingly diagnostic to the expert roentgen fluoroscopist There is usually slight, but sometimes considerable, regurgitation of blood during systole producing an apical systolic murmur which is transmitted to the axilla There are no valves in the pulmonary veins and pressure is reflected back into the pulmonary circuit and rises generally throughout the pulmonary system and in the capillaries giving rise to conspicuous congestion Peripheral resistance thus increases, and there is a rise in the blood pressure in the great pulmonary artery and this is reflected against the closing pulmonic valve giving rise to the characteristic accentuation of the pulmonic second sound This accentuated P is palpable as a diastolic shock in the second left interco tal space

The stretched and hypertrophied left atrium compensates by a greater stroke and more continuous atrial systole in an attempt to complete the filling of the cavity of the left ventricle The diastolic volume of the left ventricle seems to decrease which contributes to the sharp accentuation of the mitral first sound The rise in the pulmonary blood pressure must be borne and compensated for by the increased functional activity of the right ventricle

The right ventricle responds with an increasing stroke volume dilatation and myocardial hypertrophy This adds to the already high pressure in the pul monary circuit The rising pulmonary hypertension seems to help the left atrium in its attempt to force an adequate amount of blood through the mitral orifice into the left ventricular cavity How surprisingly well this is accomplished often is demonstrated at the autopsy table There is sometimes found only a minute slit fish mouth or button hole opening at the apex of a taut fibrous diaphragm of the fused thickened mitral leaflets One must conclude that a very small vol ume of blood at best could have passed during each diastolic period The right ventricle eventually fails under the strain and a relative tricuspid insufficiency develops The systolic tricuspid murmur may not be heard but the engorgement and systolic pulsation of the neck veins and of the liver develop

As the pulmonary pressure increases, the whole system dilates and even the pulmonic valve may dilate so much under the considerable back pressure that a relative pulmonic insufficiency of moderate to severe grade develops This gives rise to the Graham Steell[64] phenomenon with basal high pitched diastolic mur mur which is propagated downward along the left sternal border In rare cases in which there is a slight congenital hypoplasia of the foetal slit valve a defect in the interatrial septum may be opened by the extreme pressure in the left atrium

incident to mitral stenosis The retrograde junction of this foetal pathway results in dilatation of the right atrium to complete at least one form of Lutembacher s syndrome

The chronic dilatation of the left atrium occasionally in very severe cases of mitral stenosis with its constant pressure causes atrophy in the more or less triangular pad of adipose tissue in the atrioventricular groove about the circumflex branch of the left coronary artery During further rises in intraatrial pressure there may be temporary obliteration of the coronary lumen This with other changes in the coronary system the results of the previous rheumatic arteritis and possibly aortitis may cause enough coronary insufficiency to produce an anginal syndrome

The peripheral systolic blood pressure particularly is lowered and the pulses usually are reduced in size In those patients in whom there has been an unusual amount of rheumatic pulmonary arteritis the greatest degree of right ventricular enlargement appears In mitral stenosis oxygenation of the blood is less efficient and the grade of unsaturation increases producing a slight cyanosis which presents high over the cheek bones the nose and the ears Greater oxygen utilization due to slowed circulation in the periphery increases the oxygen unsaturation Furthermore catheterization of the right atrium in patients with mitral stenosis has demonstrated partial obstruction of the superior vena cava as another cause of the mitral facies[44]

The dilated pulmonary artery rather than an engorged left atrium may cause enough pressure on the recurrent laryngeal as it loops under the arch of the aorta to result in partial or complete paralysis of the left vocal cord with consequent hoarseness dysphonia and aphonia in rare cases[9, 69] Pathological dilatation of the left atrium results in changes in the muscle so that the wavelike spread of the excitatory process is interfered with and the normal sinoatrial mechanism sooner or later is replaced by a circus mechanism of atrial fibrillation

The stasis of the blood in the dilated left atrium particularly after fibrillation has set in is conducive to thrombus formation Usually a clot begins to form in the left auricular appendage and adheres between the musculi pectinati or trabeculae carnae Occasionally small masses break off from the thrombotic mass in the atrium and pass to the left ventricle and are carried out into the blood stream This results in embolism in the greater system frequently in the brain but occasionally in other organs or in the peripheral arteries In rare instances the thrombus becomes detached and accumulates as a free round mass in the atrium This ball thrombus may roll into the funnel or fibrosed mitral valvular diaphragm and temporarily obstruct the flow of blood into the left ventricular cavity to produce the so called *ball valve thrombus attacks*[71]

Roentgenological exploration of the chest often will demonstrate that dilata

tion of the left atrium and pulmonary root produces a prominent bulge on the left border of the heart So man h diagnosed mitral disease on fluoroscopic study that has been missed by the clinical experts at the Brigham Hospital Levine in the reexamination of some of these cases could not demonstrate the characteristic physical signs

In an occasional case of mitral ten is the left atrium enlarges to such an extent that it extends to the right and replaces the right atrium as the right border of the heart The rumble may be heard in rare instances at the right lung base and axilla posteriorly The esophagus likewise is displaced to the right and backward sometimes to the left The pressure on the esophagus may cause dysphagia

Calcium deposition in the mitral and aortic rings may be recognized during fluoroscopic examination (Sosman and Wosik) In the fluoroscopic studies of calcified atrioventricular valve rings Sosman and his associates and others have been impressed by the conspicuous movement of the atrial floor toward the apex in the shortening of the long axis of the heart during systole

The stages of mitral stenosis by virtue of the tendency of its mass of scar tissue to contract gradually, advance progressively This progress of the valve lesion is associated with serious complicating abnormalities It is of some importance in prognosis to be able to recognize the degree of stenosis Since Broadbent s classic writing three or four stages in the evolution of mitral stenosis are described on more or less arbitrary grounds Early moderately advanced and extreme degrees should be identified though admittedly the stage limits are difficult to establish absolutely

In the early stages with the functioning orifice remaining about 7 cm in circumference and 450 sq mm in area with relatively flexible valve leaflets the flow of blood is obstructed but slightly, and there is little embarrassment to the pulmonary circulation A short low pitched, late diastolic or presystolic rumbling sound alone may be heard in the area of the sharply circumscribed apex beat Often this is brought out only by putting the patient through some exercises and then having him promptly assume the left lateral position This throws the heart against the anterior lateral chest wall and facilitates the propagation of the rumble to the chest wall, to the stethoscope and thus to the ears

Aortic Regurgitation

Aortic regurgitation produces the most striking cardiovascular signs The imperfect apposition of the aortic cusps permits regurgitation of small or large amounts of blood up to one half of the systolic output of the left ventricle The rapid back flow of blood from the high systemic systolic pressure through the

defective valve results in a high pitched often musical, diastolic murmur The blood returned into the cavity of the left ventricle during the diastolic period dilates it The stretching of the scroll muscles seems to be a stimulus to increased activity and compensatory increase in the systolic output Fortunately sudden left ventricular strain of experimental aortic insufficiency or that of rupture of an aortic valve cusp occurs rarely Valvular incompetency usually begins insidiously and develops slowly so that the adaptive mechanisms may come into play and compensatory changes develop with the evolution of the defect Gradual dilatation seems to afford an increasing stimulus to ventricular activity enlargement dilatation and hypertrophy

The regurgitation from the aorta into the left ventricle results in a failure of the sustaining of pressure in the aorta during ventricular diastole The pressure in the left ventricle rises The diastolic intraventricular tension and heart volume increase and stretch the scroll muscle Increased pressure and dilatation and consequent added work along with the probable decrease in coronary blood flow all act as stimuli to cardiac hypertrophy A much larger volume of blood flows in through the widely open normal mitral orifice during diastole than usually regurgitates through the aortic defect This is particularly so if the lesion is slight and the myocardial tone is good The output of the left ventricle per beat or the stroke volume increases or rises

There is some loss of the effect of the elasticity of the aortic wall in the maintenance of the circulation A compensatory rise of the systolic blood pressure a the diastolic level drops and the consequent increase in the pulse pressure are characteristic of aortic regurgitation As a result of these pressure changes throbbing is noted in the peripheral vessels Corrigan s sign is noted in the bounding carotids with De Musset s nodding of the head with each systole and the quick collapsing water hammer pulse in the brachials and in the radial arteries at the wrists This is the traditional pulsus altus et celer

The peripheral arteries in free aortic regurgitation almost collapse in diastole and the head of the systolic wave produces a sharp click which has been called the pistol sound or a double sound may be heard Traube s sign Furthermore when aortic regurgitation is free the total arterial column of blood seems to move backward in diastole and this gives rise to the diastolic murmur of Duroziez[65] which is heard often in the partially compressed peripheral arteries The unsustained and elevated systolic pressure is higher in the legs and shifts with the change from the supine to the upright position The throbbing is propagated into the periphery and even to the capillaries, which dilate and show definite throbbing the so called capillary pulse The retinal arterioles do likewise

Overactivity of the left ventricle is noted as a diffuse heaving impulse against the left chest wall in the lower left apical area Regurgitation primarily through

the posterior sector of the aortic ring past a deformed posterior cusp produces the Austin Flint phenomenon [1] In this the regurgitant stream is directed against the anterior mitral leaflet and the septum This usually drives the anterior mitral sail up into the atrioventricular orifice impinges it between two streams and thus produces a functional obstruction to the flow of blood from the left atrium to the left ventricle with a rumbling diastolic murmur at the mitral orifice

Regurgitation primarily through the anterior sector of the aortic ring, past one or both damaged anterior cusps may be recognized as Belthasar Foster's syndrome with the high pitched diastolic murmur transmitted unchanged to the apex and to the left axilla The regurgitant stream in diastole strikes the free wall of the ventricle and does not interfere with the valve action

The folding downward of the right anterior aortic cusp into the regurgitant stream produces an unusually loud whistling, sawing humming musical or cooing diastolic murmur, the bruit de scie of Hodgkin Key and others Often this is audible at some distance from the patient's chest without the use of a stethoscope Bellet, McMillan and co workers have corroborated Hodgkin's observations of many years ago namely that retroversion or eversion or forward collapse of the right anterior aortic cusp may take place and give rise to a pathognomonic or characteristic diastolic murmur This loud, cooing or sawing murmur, best heard in the third left parasternal space frequently has been erroneously thought to be diagnostic of a perforated aortic cusp or an intracardiac arteriovenous communication This murmur gradually decreases as the aortic regurgitation increases, due to the progressive rolling downward usually of the top heavy, right, anterior cusp but sometimes also of the other aortic leaflets

Conspicuous regurgitation accompanies syphilitic aortitis and is due in a large measure to dilatation of the aortic ring with broadening of the commissures at the point at which the cusps are attached The proliferative process, that results from the mechanical irritation of the regurgitant stream begins in the commissures and spreads out along the free edge of any one of the cusps and adds to the defect in cases of long standing The cusps already short from the fusion with the intima at the commissures thicken further and roll down to aggravate the dysfunction of both the segments as well as the incompetency due to the general dilatation Rheumatic aortic valvulitis rarely is accompanied by much rheumatic aortitis and dilatation of the aorta The rheumatic aortic cusps are, however usually more extensively sclerosed and often calcified and rigid producing concomitant aortic stenosis

It is to be remembered that the coronary arteries originate in the two anterior sinuses of Valsalva Whenever one or both of the anterior aortic cusps are rolled back, the defect is primarily in the more important anterior sector Irrigation of the coronary bed then most often is considerably impaired The turning down

ward from the top or free border of the reflecting cusp and the low diastolic blood pressure together contribute to decreased coronary blood flow These patients even though relatively young often present Lewis syndrome of anginal failure and sudden death is not infrequent in this type of aortic regurgitation

In free aortic regurgitation the movement of the blood column is at high velocity and thus produces vibrations of high frequency and consequently high pitched diastolic murmurs The heart rate tends to increase apparently in an attempt to shorten the diastolic period The left ventricle must bear up under considerable strain The blood flow to the brain is maintained with some difficulty and in sudden failure as in rupture of an aortic cusp cerebral anemia develops rapidly Some left ventricular weakness sooner or later develops and the resulting disturbed circulation to the respiratory center often gives rise to Cheyne Stokes breathing and paroxysmal nocturnal dyspnea

Aortic Stenosis

Aortic stenosis does not produce such conspicuous cardiac and circulatory dynamics as aortic regurgitation The reduction of the normal aortic circumference of 7½ cm with an area of 450 sq mm to 7 cm and 400 sq mm or less will interfere significantly with the ejection of blood from the left ventricle into the aorta The very nature of the valvular disease makes the process insidious and inconspicuous It presents itself in slight grades and particularly associated with an equal grade of regurgitation A high grade of aortic stenosis usually takes at least years and sometimes decades to develop Calcification of the aortic ring and the fibrosed cusps frequently is so extensive that it can be seen in routine radiological fluoroscopic studies The designation aortic stenosis with calcification or calcareous aortic valvular disease is applied to this condition by Christian and Margolis and associates[34]

Stenosis is much slower in developing in the aortic than in the mitral valve The obstruction to the outflow of blood from the left ventricle results in a rise in the intraventricular pressure The slow prolonged ejection of blood through the narrowed orifice causes vibration of the scar tissue at the aortic root giving rise to the characteristic systolic thrill and systolic murmur These are propagated in the direction of the blood flow into the neck vessels

The peripheral systolic blood pressure is low and the diastolic remains about the same the pulse pressure is decreased and the aortic second sound diminished in intensity The period of ventricular discharge is slow and prolonged and the pulse waves rise slowly to a plateau Often a double effort seems to be necessary the first to stretch the orifice and the second to propel the blood flow into the aorta This produces the anacrotic wave or the notch on the slow upstroke the

double humped and the plateau pul e The left ventricle seems to have to exert a good deal of energy in overcoming the obstruction Then apparently there seems to be secondary augmentation due to the continued powerful thrust of the ventricle Con iderable vibration of the fibrosed, thickened, aortic root results

The impediment to the outflow of blood from the left ventricle through the aortic orifice in aortic stenosis is well borne until it reaches a very advanced stage, unless it is associated with obstruction of the coronary orifice The thick wall of the left ventricle seems to be able to overcome the obstruction and maintain a fairly adequate circulation particularly when the stenosis develops rather in sidiously as it usually does The scroll muscles surrounding the left ventricular cavity are stretched some and apparently some temporary dilatation occurs High pressure develops in the left ventricle varying in grade according to the obstruction, and concentric hypertrophy usually develops

The coronary orifices usually are more or less involved in the process This encroachment leads to coronary insufficiency with the development of symptoms of anginal failure The pulse is slow There is often a hyperactive carotid sinus reflex when the carotid sinus is stimulated, and cerebral anemia frequently de velops Circulatory equilibrium seemingly is maintained for long years in many cases but angina pectoris and sudden death may intervene

Tricuspid Insufficiency

Tricuspid insufficiency usually presents visible disturbances in circulatory dynamics The lesion more commonly is functional rather rarely organic The tricuspid is spoken of often as the safety valve for the engorged pulmonary sys tem It is not exactly this since its giving away affords only temporary relief Failure of the tricuspid leaflets to be approximated and the consequent insuf ficiency result in regurgitation from the right ventricle into the right atrium A blowing systolic murmur, localized in the fourth left interspace in the parasternal line usually is produced The intraatrial pressure rises and the rise is trans mitted back through the superior and inferior venae cavae to the great venous channels since there are no competent valves in these veins The lack of the venous valves creates an awkward situation and makes compensation more dif ficult Increased venous pressure becomes evident in the distended neck vein and in the engorgement of the liver

The stretching of the right atrium stimulates the muscle of the wall to greater contraction Most of this effort however is futile in the presence of relatively unguarded caval orifices The rising venous pressure in the engorged atrium will help some in increasing filling of the right ventricle and in augmenting its criti cally low output The venous blood column in direct communication with the

right ventricular cavity rises with each systole The positive systolic pulsation is visible in the neck veins and palpable in the expanding movements of the engorged liver The blood pressure and flow in the pulmonary circulation and the intensity of the second sound in the second left intercostal space are decreased Increased venous pressure is a stimulus to effectively increased peripheral resistance

If the efficiency of the right ventricle falls off pulmonary irrigation and consequently blood aeration becomes less efficient and anoxemia results The incompetency of the tricuspid valve is therefore significant and compensation always is considerably subnormal thus the disturbance is poorly borne Cyanosis with compensatory polycythemia may develop There are increasing venous back pressure effects engorgement of the liver the kidneys the neck and the head Jaundice may develop to give a peculiar greenish tinge to the bluish facies The engorged liver often becomes the seat of cardiac cirrhosis and abdominal ascites precedes edema of the legs

Tricuspid Stenosis

Tricuspid stenosis disturbs the cardiodynamics by extreme back pressure effects in the systemic circulation and decreased blood flow in the lesser system The tricuspid valve rarely develops the grade of obstruction that is seen usually in the rheumatic mitral valve It is rare indeed to have a patient with pure tricuspid stenosis only Concomitant insufficiency usually is present just as there is some insufficiency as well as stenosis in mitral disease and often also in aortic disease A healing of inflammatory valvulitis of the tricuspid valve usually produces more insufficiency than stenosis therefore the stenosis adds some to the impediment or the defect

A constriction of the tricuspid orifice from its usual 10 to 12 cm in circumference and 600 to 700 sq mm area to less than 8 cm diameter and less than 500 sq mm area would interfere with the free flow of blood through the valve The embarrassed blood flow gives rise to the low pitched rumbling diastolic murmur in the fourth or fifth interspace near the sternum The effects of slight tricuspid obstruction are added to the abnormal cardiodynamics of tricuspid insufficiency

The rarely encountered significant grade of pure tricuspid stenosis increases intraatrial pressure and causes the rise to persist in diastole as well as in systole The effect of the augmented systolic atrial contraction is a presystolic A wave which is reflected up into high and often visible levels in the neck veins and down into the liver The venous stasis and partial asphyxia initiate reflex peripheral vasoconstriction which sustains the blood pressure at fairly normal levels The

right atrial muscle dilates and hypertrophies, but it is only moderately effective in compensating for the defective function of the tricuspid valve Atrial fibrillation may develop to further embarrass the circulation

The obstruction at the tricuspid ring interferes with the filling of the right ventricle thereby decreasing its systolic volume output This contributes to the lowering of the tension in the pulmonary circuit and consequent inadequate oxygenation of the blood The pulmonic second sound is decreased in intensity Some adjustment usually occurs in increased concentration of hemoglobin and in increased number of red blood cells in an effort to augment the carrying capacity for oxygen of each cubic millimeter of blood This makes up some for the reduction in the pulmonary circulation

The hematological changes result in increased viscosity of the blood, and this adds to the burden of the heart Chronic persistent engorgement of the great veins of the neck and head as well as of the liver will give rise to a dusky, greenish, icteric cyanosis of the facies Chronic engorgement of the liver leads to cardiac cirrhosis and ascites develops early usually long before there is dependent edema of the extremities The cardiac mechanism usually is not disturbed until late unless there is a higher grade mitral disease to produce an imbalance in intraatrial pressure, and then atrial fibrillation often is precipitated earlier

Pulmonic Regurgitation

Pulmonic regurgitation produces abnormal circulatory dynamics in the lesser circulation just as aortic regurgitation does in the greater circulation The back flow through the incompetent pulmonic valve into the right ventricle gives rise to the high pitched diastolic murmur that is transmitted toward the sternum and along the left sternal border to the xiphoid In the presence of pulmonic regurgitation the pressure in the pulmonary artery is poorly sustained during diastole, and the pulmonic second sound is decreased and usually lost in the murmur

The increased filling of the right ventricle evokes a greater stroke with a consequent rise in the systolic pulmonary pressure The pulmonary artery dilates, and pulmonary pressure, therefore, is increased also There are produced strikingly abnormal dynamics in the major pulmonary system The characteristic phenomena, the throbbing pulmonary artery or dancing hilar shadows at the lung roots are demonstrable only in roentgen fluoroscopic studies The throbbing in the pulmonary arterial system or in the bronchovascular tree incident to this increased pulse pressure unfortunately is seen only occasionally The minute volume of blood flow through the lungs is decreased and blood aeration consequently is subnormal

The increased filling tension and stretching of the right ventricle are apparently a stimulus to augmented cardiac action and hypertrophy which help to maintain the pulmonary flow and thus keep the oxygenation at fairly adequate levels for years in some cases The right ventricular enlargement and hypertrophy increase the transverse diameter of the heart some but rotation takes place so that the right ventricle makes up the whole anterior surface of the heart Some grades of pulmonic regurgitation are thus seemingly well tolerated and more so than a similar defect in the aortic valve This is primarily because there are normally no coronaries to be flushed from the pulmonary artery The pulmonic valve circumference is normally 8 cm and the cross section area is about 500 sq mm

Pulmonic Stenosis

Pulmonic stenosis of an acquired type is rare and so is also the pure congenital type The reduction of the pulmonic orifice to a 6 cm circumference and an area of 300 sq mm or less obstructs the outflow from the right ventricle This causes the systolic vibration or thrill from the fibrosed valve and the systolic murmur heard in the second left interspace The regurgitant stream from the pulmonary artery rarely interferes significantly with the opening of the tricuspid valve

The abnormal dynamics again are not very conspicuous Gradual increase of the obstruction and gradual distention of the right ventricular cavity with increased pressures in the right ventricle develop The right ventricle with its thinner wall may be damaged and stimulated to hypertrophy to overcome the increasing grade of stenosis of the pulmonic orifice The stretching that results helps some to overcome the obstruction during the period of ejection which is slow and prolonged Dilatation of the right ventricle with a secondary augmentation and an increased stroke follows This is the stimulus furthermore to great eccentric hypertrophy of the right ventricle greater than that of mitral stenosis with secondary pulmonic insufficiency The tricuspid valve may become secondarily insufficient and add further embarrassment to the circulation

In spite of an augmented stroke and compensatory hypertrophy of the right ventricle the blood flow usually is not sufficient to maintain the necessary minute volume in the pulmonary system for adequate aeration of the blood Complete or 95 per cent or 20 volumes per cent oxygen saturation therefore is not accomplished The resulting anoxemia is the stimulus to the development of a moderate to a rather high grade of secondary polycythemia There is with the increase in hemoglobin and erythrocyte counts unfortunately also an increase in the blood viscosity

The Circulatory Dynamics of Combined Valvular Lesions

Rheumatic valvulitis usually has been considered to result first in incompetency or insufficiency of the mitral valve and then later develop slight to marked obstruction of mitral stenosis St Lawrence has questioned this and reported a series of primary mitral stenosis cases Organic mitral disease, however, practically always presents a combination of some obstruction and some regurgitation The resulting pathological physiology depends in a large measure upon which lesion predominates Stenosis along with insufficiency of the mitral valve increases the pressure in the left atrium and causes it to dilate more Stenosis increases further the blood pressure in the pulmonary system and tends to make it persistent throughout systole and diastole The regurgitant stream from the ventricle is transmitted into the atrium and is reflected back through the pulmonary veins to the capillary beds increasing the pulmonary pressure and added obstruction in the mitral ring causes conspicuous rise in the back pressure in the pulmonary arteries This is evident in the greatly intensified pulmonic second sound and visible pulsations of the dilated pulmonary arterial root

In a combined lesion the regurgitant stream to the atrium causes the blowing systolic murmur, while obstruction of the flow from atrium to ventricle gives rise to the diastolic rumble Both murmurs are heard best immediately over the apex The systolic murmur is transmitted into the axilla while the diastolic rumble usually is sharply localized to the area of the apical impulse or slightly above and inside the point of maximum impulse The pulmonic second sound probably is more accentuated than it would be from stenosis alone but this is impossible to establish A double lesion especially with a high grade mitral stenosis is associated with much hard scar tissue with few blood vessels while the very free mitral insufficiency usually is associated with greater vascularity of the valve leaflets This or some other factor makes patients with mitral insufficiency much more prone to secondary subacute bacterial endocarditis than are those with pure mitral stenosis

The combination lesion apparently is a greater strain than a single lesion but this depends particularly upon the grade of incompetency produced Mechanism disturbances are more common in mitral stenosis than they are in mitral insufficiency and most frequent in the combined defects

Combined tricuspid valvulitis occurs in about 35 per cent of the patients that have double mitral lesions When the tricuspid valve is involved recognizably there is practically always also mitral and aortic disease The tricuspid lesions rarely are of sufficient magnitude to give striking signs or to produce great changes in the cardiodynamics The systolic murmur of tricuspid insufficiency is heard not uncommonly but the rumble of tricuspid stenosis is not often elicited Tri

cuspid lesions produce peripheral venous manifestations such as engorged neck veins and liver and some edema If the disturbances are of any significant grade there might even result a fall in the pulmonary blood pressure from a decrease in the filling and in the output of the right heart This would relieve partially the active pressure part of pulmonary engorgement When relative or functional tricuspid insufficiency develops in the course of congestive heart failure there is often a temporary relief of dyspnea It is for this reason that the tricuspid insufficiency is termed a safety valve effect

Aortic regurgitation most often practically always is associated with mitral valve lesions Aortic regurgitation causes the dilatation of the left ventricle which may affect favorably the mitral stenosis by stretching it some and allowing a greater flow of blood into the left ventricle At the same time mitral insufficiency may be increased and the back flow into the left atrium occasionally may outweigh the beneficent effect of the increase in size of the narrowed orifice The inadequate filling of the left ventricle along with shunting during ejection contributes to decreased cardiac volume output The systemic blood pressure consequently does not rise so high during systole and the consequent fall in the pulse pressure relieves some of the throbbing in the peripheral vessels seen in uncomplicated aortic regurgitation

Regurgitation through the posterior sector of the aortic valve may produce some obstruction of the flow into the left ventricle The combination of this defect therefore naturally will aggravate the disturbances of mitral function and thus it may modify the cardiodynamics considerably Sometimes it seems to improve the situation so that the combined lesions are borne better than single ones A decrease in peripheral phenomena may lead some to mistake the basal high pitched diastolic murmur for a Graham Steell murmur The position and propagation however along with low diastolic pressure in the periphery will rule against such an interpretation Again the rumbling diastolic murmur at the apex in the presence of a basal high pitched murmur sometimes must be considered a functional mitral stenosis instead of true organic mitral disease A history of rheumatic fever in some form often will determine the diagnosis to be organic mitral disease

Aortic regurgitation particularly that of rheumatic etiology is associated with aortic stenosis of some degree more often than was previously thought On the other hand aortic stenosis is rarely to be found without some slight regurgitation *The development of aortic stenosis in an already incompetent aortic valve* will change the cardiodynamics and modify the pathological physiology particularly with respect to the peripheral phenomena of free aortic regurgitation The high systolic fling that causes the carotid throbbing is decreased in height but the diastolic level is affected only slightly if at all or changes very little if any

As the stenosis of the aortic valve increases the dynamic effect on the pulse is expressed in decreased rate and a low rising and plateau character These peripheral phenomena the exact antithesis of those of the regurgitation, gradually modify the character of the pulse The height and quickness of the pulse of aortic regurgitation are decreased and the peripheral throbbing becomes less evident In the presence of aortic stenosis a systolic murmur and thrill usually develop in addition to a high pitched diastolic murmur which rarely is accompanied by a thrill Heavy calcium depositions in the valve make the sounds more strikingly abnormal and reverberating The calcification of the aortic root is demonstrable in fluoroscopic x ray studies and the diagnosis of calcareous disease of the aorta is justified on the finding of irregular shadows at the root of the aorta The pistol shot the double sound of Traube and the diastolic murmur of Duroziez in the compressed femoral are distinctly decreased in intensity and sometimes become inaudible The pulse pressures of course are cut down from their previous high grade, and the Corrigan water hammer and capillary pulsations are less striking and less conspicuous

General Symptomatology of Chronic Cardiac Valvular Disease

Chronic cardiac valvular disease certainly in its earlier stages is practically asymptomatic and usually remains so in nervously stable individuals until congestive heart failure develops The absence of symptoms frequently delays for many important years the recognition of the presence of a valvular defect Symptoms may develop very insidiously but often come on suddenly with a patient who had complained of no significant disturbances until he has overexcited himself or has suffered from an acute infection Symptoms are never pathognomonic and only now and then suggestive of the exact type of valvular defects from which the patient is suffering It is usually the intervening myocardial insufficiency which gives rise to symptoms in the stolid patient with a crippled heart valve

Sometimes very close questioning will bring out previously unrecognized symptoms in a sensitive individual before the appearance of the signs of myocardial insufficiency Leading questions may bring on symptoms in a patient who has never previously had a complaint until his attention was so directed by questions This is primarily true because the patient in the early stages of cardiac disease had not been observing his reactions to effort carefully Occasionally direct and abrupt questioning by a tactless physician may lead to the development of a cardiac neurosis in a patient who has a slight organic valvular and myocardial dysfunction of which he was totally unaware It is well known that patients with pure cardiac neuroses with neurocirculatory asthenia mild hyperthyroidism anemia nephrosis varicose veins or emphysema may present

respiratory and general symptoms that are indistinguishable from those of patients with heart disease

In a patient with chronic cardiac valvular disease the time of onset and the rate of development of symptoms once they have appeared depend upon many factors The amount of myocardial damage, that was done at the time of the causative infection or that had resulted from the disturbances in the coronary circulation incident to the lesion or to blood pressure changes, probably is of first importance The position of the valve that is involved as well as the extent of the damage to the valve must play some part The amount of physical exertion that the patient has done especially when he is not in training but even when he is in good physical condition may determine to a considerable extent the rate of development of the symptoms

A history of exposure to sudden strain out of the ordinary routine of the individual is quite as important as is the extent of physical effort that the patient has been doing routinely or has accomplished day in and day out Precipitating factors always should be sought for It must be remembered that increase in the blood pressure incident to nervous strain psychic shocks mental upsets and worry may bring on trouble Trauma exposure to elements and infections with a detrimental effect upon the heart muscle may upset the myocardial reserve and hasten the appearance of symptoms The nervous stability of the patient determines the level at which symptoms appear In the hypersensitive neurotic individual symptoms appear upon slight provocation and much earlier than in the phlegmatic stolid individual If the patient gets panicky symptom development may be more rapid

Symptoms and Associated Valvular Disease

General palpitation breathlessness cough and expectoration are non specific symptoms often caused by conditions other than valvular disease and may appear almost as often in one type of valvular disease as in another Nevertheless there is some suggestion in the intensity of the development of symptoms and accompanying findings as to what valvular lesion a given patient may be suffering from There are no absolutely characteristic or pathognomonic symptoms in the early stages of chronic cardiac valvular disease Occasionally a very sensitive patient may note subjective manifestations that are suggestive of aortic regurgitation or of mitral stenosis and in very rare instances of tricuspid stenosis A valvular lesion must be of considerable grade to call forth diagnostically suggestive or pathognomonic symptoms

Aortic regurgitation with or without stenosis of a very free type sometimes gives rise to suggestive symptoms because of the striking exaggeration of the cir

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Further Elaboration of Cardinal Symptoms

Palpitation a consciousness of rapid, slow or augmented regular or irregular heart action on or after exertion or under emotional stress is a common complaint of nervous individuals but also is common in patients with heart disease The sudden speeding up of the heart sharp dropping off of the rate and irregularity as well as an anxiety state could account for this symptom and should be considered in the differential diagnosis An abnormal sensitivity to heart action is noted often on lying down in bed at night Attacks may come on as regular paroxysms while a patient is at rest as in the presence of atrial flutter of paroxysmal tachycardia or of irregular palpitation of transient atrial fibrillation These should call for careful auscultation between attacks over the apex in the left lateral position for the characteristic rumble of mitral stenosis In vagotonic individuals sinus arrythmia and bradycardia or heart block may give rise to the sensation

Dyspnea i e noticeably increased shortness of breath caused by effort or activity which previously has been accomplished without any discomfort is a suggestive symptom It is usually gradual in its development but may be precipitated by sudden exposure to physical or emotional strain or come on abruptly for no obvious reason Aortic valvulitis is prone to present paroxysmal nocturnal dyspnea as an early symptom, while mitral disease even in the presence of advanced lesions fails to induce dyspnea except after considerable exertion The initiation of the Hering Breuer reflex and rapid shallow breathing by increased alveolar tension on inspiration may be suppressed promptly by morphine This is true dyspnea which is confused with ineffectual expiration found in obstruction in the respiratory tract as in asthma or loss of lung elasticity due to fibrosis or the full deep breathing of acidosis or the sighing respiration of psychological origin Dyspnea on effort usually is present in individuals with valvular defects and in these often it is evidence of pulmonary congestion and the beginning of congestive heart failure with a decrease in vital capacity In sudden or severe attacks the patient usually feels the irresistible urge to assume the sitting position to relieve the respiration distress Such orthopnea usually occurs only in congestive heart failure Decrease of the blood flow through the brain tissues especially the respiratory center contributes to the initiation of Cheyne Stokes breathing and paroxysms of nocturnal dyspnea These usually are evidences of left ventricular failure rather than the result of abnormal mechanical shifts in the movement of the blood mass incident to a valve lesion

Hyperesthesia or *hyperalgesia of the skin* over the left anterior and lateral chest wall is associated most commonly with radiculitis from spinal arthritis and more frequently erroneously than correctly suggests heart disease It may occur

culatory dynamics with resulting decreased cerebral and coronary circulation Such symptoms as giddiness vertigo faintness syncope, insomnia, mental confusion, headache precipitate or nocturnal dyspnea cardiac ache, retromanubrial burning or choking constriction or smothering precordial distress, substernal oppression angina pectoris epigastric palpitation, pain, dyspnea or cardiac asthma the latter usually appearing in paroxysms Conspicuous throbbing of the carotids and peripheral vessels disturbs some patients Palpitation probably is most marked in those with free aortic regurgitation but paroxysms of tachycardia may produce similar effects

Mitral stenosis with or without insufficiency of high grade is accompanied by pulmonary engorgement and dilatation of the pulmonary artery sometimes with compression of the recurrent laryngeal nerve Complaints of cough, hemoptysis, hoarseness dysphonia or aphonia suggest the presence of mitral stenosis Dilatation of the pulmonary artery is primarily responsible for the laryngeal nerve irritation and paralysis but dilatation of the arch of the aorta may produce similar symptoms Dilatation of the left atrium may encroach upon the esophagus producing dysphagia and compress the superior vena cava to intensify the cyanotic flush and orange lips Palpitation is a common symptom The pulsation which is being felt is often irregular The sudden onset of paralysis or weakness on one side in an otherwise healthy individual in early adult life suggests the possible presence of mitral stenosis with a cardiac source of the causative embolus A thrombus in the dilated left atrium usually is the source from which an embolus has broken off and has been carried to a point of narrowing of a branch of the cerebral artery going to the cortex If the left atrial thrombus is large and free and occasionally becomes engaged in the mitral funnel a dramatic and terrifying train of symptoms develop peripheral paresthesia, pain, thrombosis and gangrene of the tips of the fingers and toes and syncope appear in the pulseless victim

Tricuspid disease with considerable valvular dysfunction produces early considerable engorgement of the neck veins with cyanosis and engorgement of the liver with jaundice Acute congestion in the gastrointestinal tract with resulting nausea abdominal distention, ascites and vomiting may appear There may be a sensation of fullness in the neck and usually there is drowsiness sometimes striking abdominal distress and occasionally a peculiar blue green facies Adherent pericardium produces somewhat the same clinical picture

Congenital heart disease cases complain frequently of a feeling of fullness in the vascular system In these blueness often has been present since birth and is most striking Palpitation drowsiness sluggishness and unusual susceptibility to infections of the respiratory tract are suggestive of but not necessary for, the diagnosis of congenital disease

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probably as the result of sensitization of the respective segments of the spinal cord by a bombardment of impulse from an enlarged aorta or heart, which may be the result of valvular disease It may be termed a precordial or substernal neuralgia and may result also from spasm and distention of the esophagus, stomach or splenic flexure of the colon A sense of fullness in the neck with engorgement of the veins may appear earlier in the presence of tricuspid stenosis or obstruction of the superior vena cava than is evidence of non specific myocardial insufficiency

Precordial or *substernal cardiac pain* is common in patients with acute rheumatic heart disease It is of a prickling quality in pericarditis and burning in aortitis Valvular diseases may be responsible for dull aching of considerable intensity the result of enlargement with distention of the heart chambers Occasionally typical anginal paroxysms of an extreme grade may appear Lew has pointed out the frequency of angina in patients with free aortic regurgitation, but it may also occur as Sternberg has noted in mitral stenosis cases In both types the pain is due to sharp changes in coronary flow, the result of lowered diastolic pressure in aortic regurgitation and of lowered systolic output in mitral stenosis In the latter condition possibly it is due also to compression of the circumflex nerve by extreme engorgement of the left atrium

Epigastric distress sometimes may be the first symptom of which the patient with mitral or tricuspid disease complains It usually is accompanied by a sense of fullness in the upper abdomen and sometimes the edge of an engorged, congested liver is felt by the patient This may be the first indication that the patient has of the presence of tricuspid stenosis or mitral stenosis That is usually, of course, the first sign of congestive heart failure of any etiology There is a peculiar bluish green discoloration due to the combinations of cyanosis and jaundice which is characteristic of tricuspid stenosis

Cardiac asthma with acute pulmonary edema is most common in left heart failure but often may appear suddenly also in patients with aortic regurgitation It occurs fairly frequently in mitral stenosis but probably most commonly in hypertensive heart disease *Ascites* developing before edema of the extremities suggests tricuspid stenosis but it occurs also in adhesive pericarditis and in portal hepatic cirrhosis *Swelling of the extremities* a *decreased output of urine* *fever* and *exhaustion* are common symptoms of any type of congestive heart failure

Fever in a patient with valvular heart disease is strongly suggestive of secondary subacute bacterial endocarditis However any type of congestive failure may be accompanied by a slight rise in the body temperature It drops off as soon as the circulatory equilibrium is restored by rest in bed and digitalization Patients with valvular disease and congestive failure probably are more likely to

have fever than non valvular cases, but it usually does not amount to more than one degree The *sense of excessive fatigue or exhaustion* may be conspicuous particularly it the presence of fever as the first symptom of beginning heart failure

The sameness of symptoms becomes most conspicuous in all types of heart disease when coronary and myocardial insufficiency intervene Congestive heart failure seems to contribute similarly in all types of valvular disease to restless ness prostration epigastric oppression anorexia nausea, vomiting dyspnea, orthopnea cyanosis jaundice and edema of the body

Symptoms constitute a good index of the functional capacity of the heart The cardiac patient gradually becomes aware of the limitation of his activity and his circulatory equilibrium is rather precarious His reaction to the ordinary activities of life are an accurate gauge and constitute the most rational index test of the efficiency of his heart

Physical Signs

Inspection

A careful physical examination reveals suggestive and pathognomonic signs of each valvular lesion These signs advantageously may be described in general and later listed only among the cardinal signs It is desirable that each patient be studied systematically by all traditional routine methods as inspection includ ing fluoroscopic roentgenology palpation percussion and auscultation before concluding the diagnosis of the presence of a pecific valvular lesion or the absence of evidences of organic valvulitis Inspection will reveal *facies* that are very suggestive of one or another type of valvular lesions A cyanosis of the high malar region with unnaturally dark red blue lips strongly suggests the presence of mitral stenosis Pallor with or without intermittent flushing along with per haps a tinge of yellowness to the skin suggests aortic regurgitation

Cyanosis of varying grades from latent and slight to moderate or extreme strongly indicates particularly in the more intense grades the presence of con genital lesions and defects Cyanosis is the result of either decreased pulmonary oxygenation stasis in the capillaries, increased hemoglobin content or the en trance of venous blood directly into the arterial stream Normally the oxygen carrying capacity of the blood is about twenty volumes per cent Ninety five per cent saturation is maintained normally leaving only about 5 per cent or one volume per cent unsaturation The threshold value for cyanosis is about 6 vol umes per cent of oxygen unsaturation The slowing of the blood stream in the capillaries or elsewhere may result in the removal from the blood by the tissues

of more than 5 volumes per cent of oxygen, and the venous blood will be more than normally unsaturated

An increase in the total hemoglobin tends to augment the degree of unsaturation produced by decreased pulmonary oxygenation and acts in this capacity to deepen the cyanosis A decrease in hemoglobin or anemia on the other hand, for the reasons just outlined tends to lessen the cyanosis In congenital defects with venous arterial communication from the right directly to the left side of the heart, such that one third of the circulating volume of non aerated venous blood is ejected directly into the systemic arterial bed, a high grade of cyanosis is produced Extreme grades of cyanosis are produced by venous arterial shunts in the presence of obstruction of the pulmonary orifice

Pallor may be due to anemia or to a temporary ischemia of the skin and may occur in patients with chronic cardiac valvular disease as a result of the hemoglobin destruction caused by infection Apparently however pallor may be only a manifestation of reflex peripheral vasoconstriction with diminished vasomotor tone or vasodilatation in the organs in which a rich blood supply must be maintained Pallor is not a pathognomonic sign of any specific heart lesion, nor is it even a suggestive finding nevertheless it is of value in the analysis of a clinical picture

Palpation

The position of the maximum impulse of the heart s apex, whether visible or not, may be confirmed by palpation as an index of the size of the heart Friction fremitus of rheumatic pericarditis occasionally is present Palpation often reveals thrills and shocks the palpable counterparts of significant murmurs and accentuated heart sounds These one finds for the most part in mitral stenosis aortic stenosis and congenital lesions Abnormal pulsation palpable in the second left interspace may be present in congenital patency of the ductus arteriosus and in pulmonary regurgitation Aneurysm may present abnormal expansive pulsation almost anywhere All murmurs should be timed by simultaneous palpation of the carotid pulse or the apex impulse during auscultation

Significant changes in the form volume rate and rhythm of the radial and carotid pulses and of the apex beat often may be detected by palpation The poorly sustained collapsing water hammer pulse of Corrigan is found in the patient with aortic regurgitation while the patient with mitral stenosis present the exact antithesis namely a small pulse as a consequence of low pulse pressure In the presence of aortic stenosis the characteristic anacrotic double humped plateau pulse is considered by some to be essential for the diagnosis Paroxysms of high rate, auricular tachycardia flutter or the irregularity of auricular fibrillation or heart block often occur in individuals with rheumatic mitral stenosis

Careful palpation often may be sufficient to make a correct diagnosis of the type of arrhythmia present

Tenderness and palpability of the liver edge under the right costal margin as a rule indicates the presence of congestion or heart failure In rare instances a high grade tricuspid lesion may produce mechanically some enlargement of the liver Expansile pulsation of an engorged liver may be demonstrable in a rare case of tricuspid insufficiency and also in some cases of mitral stenosis The so called tricuspid diastolic thrill over the liver can be observed and recorded most rarely Edema of the dependent parts is rarely if ever, present in valvular disease until myocardial insufficiency intervenes

Percussion

Percussion further furnishes data as to the size of the heart The form of the enlarged cardiac outline often is suggestive of the type of valve lesion present An enlarged area of dullness to the left and downward is suggestive of aortic disease a snub nosed sabot or wooden shoe shaped dullness is suggestive of pulmonic valvular disease Prominence of the left atrial area of dullness suggests mitral disease while extension of the right border suggests tricuspid disease An increase in dullness in the area of the pulmonary artery suggests a congenital lesion It is impossible to determine the question of unilateral predominance of ventricular enlargement by percussion

Enlarged liver dullness hydrothorax and ascites are the end results of chronic cardiac valvular disease when congestive heart failure has intervened

Auscultation

Auscultation verifies and clarifies any palpatory findings of the disturbances of rate and rhythm that may be present and reveals accentuated heart sounds as well as the characteristic murmurs It furnishes the pathognomonic criteria of chronic cardiac valvular disease The pathognomonic auscultatory phenomena in each type of chronic cardiac valvular disease will be discussed in general and then will be arranged in the order of importance diagnostically under the respective lesion

Heart Sounds —Unmistakable deviations from the normal in the character of the heart sounds though less unequivocally established as reliable criteria than murmurs are of some importance in the differential diagnosis of the various valvular lesions The changes in the intensity and the character of the sounds are dependent upon shifts in pressure from the one circulatory system to the other These shifts in large measure are the result of cardiac valvular lesions with

consequent changes in the minute volume of blood delivered and in the ventricular output Only the most striking departures from the normal character of the sound should be regarded as significant

The accentuation of a sound indicates as a rule an elevation of the pressure or tension to which the valve is exposed and a diminution of the sound signifies a decrease in the force of closure of the valve A presphygmic period of increased pressure preceding the discharge of blood seems to be necessary for the production of an accentuated first sound Splitting and reduplication of sounds are due to abnormal, asynchronous action of two normally closely coordinated parts of the heart

Probably the most significant abnormality in heart sounds is the loud, snapping accentuation of the first sound at the apex, which is heard almost invariably in mitral stenosis often even when the diastolic rumble is barely audible The increased pressure in the right heart and against the tricuspid valve producing a high tension snap is considered by some to explain the phenomenon Others believe the contraction of the left ventricular muscle upon a partially filled ventricle and the vibration of the thickened fused often calcified mitral leaflets bearing up the static pressure of the engorged left atrium cause the sharp first sound

In mitral obstruction the accentuation of the pulmonic second sound is of corroborative value in the physical sign picture This is due to the increased pulmonary pressure from the damming back of blood into the left atrium and thence into the pulmonary veins capillaries and arteries against the pulmonic valve the conus and the right ventricle The same mechanically insufficient left ventricular filling and the consequent small systolic output allow the fall in pulse pressure with a consequent weakening of the aortic second sound

In aortic stenosis with the characteristic low pulse pressure the faint aortic second sound is of some diagnostic value The aortic second sound is greatly diminished as a result of the slow incomplete filling of the aorta A faint aortic second sound is present also in mitral stenosis in consequence of the small left ventricle output Accentuation of the aortic second sound is usual in cases of hypertension but the presence of accentuation with a reverberant liquid, metallic ring in an individual with a normal or subnormal blood pressure is strongly suggestive of the presence of an aortitis Sclerosis in the root of the aorta and aortic cusps usually involves the coronary orifices In aortic regurgitation the aortic second sound usually is replaced by a long diastolic murmur, although a faint, sharp sound sometimes remains

An increase or decrease in intensity of the pulmonic second sound is of differential diagnostic importance in congenital heart disease In pulmonic stenosis the second sound in the left second interspace is diminished conspicu

ously in intensity while in the presence of a patent ductus arteriosus there is a distinct accentuation of the second pulmonic sound

Murmurs (Organic and Functional) (Diastolic and Systolic) —Murmurs are the cardinal signs of cardiac valvular defect The rush of the circulating blood through the defectively functioning incompetent or stenotic valve into a larger chamber or lumen produces eddies and vibrations which give rise to murmurs adventitious and changed sounds thrills and shocks These signs may accompany either part of the cardiac cycle systole or diastole and the time depends upon the location of defect and whether there is obstruction to the flow or failure to hold the flow in the normal direction In rare instances an almost complete failure in closure of a valve or a very slight opening of a valve will not lead to eddy formation and no murmur will be produced Under these circumstances a diagnosis of a valvular lesion can be made only on inference or from the findings in previous or repeated examinations

The character of the murmurs depends upon the size of the opening its conformation the character of the valve borders the pressure differences on the two sides of the valve and the velocity of the flow of blood through the defect The higher and greater the difference in pressure the higher the velocity of the flow and the vibration that has been set up in the various parts the higher pitched is the murmur that results The slower the flow of blood the lower the tone of the murmur

Insufficiency of the atrioventricular valve usually produces soft blowing murmurs transmitted to the axillary base However when the regurgitant stream passes through the fibrous hard calcified opening in the rheumatic mitral valve the character of the murmur will be harsh loud rasping and prolonged and the propagation usually is to the mid axilla and left interscapular regions throughout systole but these murmurs never attain the high frequency vibration of the regurgitant murmurs from the semilunar valve

The transmission of murmurs is in the direction of the abnormal flow Propagation occurs from the base to the apex and to the axilla high up in the case of murmurs originating in and due to defects at the aortic and pulmonic orifices Transmission into the neck vessels occurs with obstruction at the aortic ring and toward the interscapular region with similar defects in the pulmonic area They are all rather high pitched in sound The low rumbling diastolic murmurs due to obstruction in the auriculo ventricular orifices usually are localized sharply in small areas

Murmurs then are signs that strongly suggest the presence of a valvular lesion but their absence does not always absolutely rule out valvulitis However not every murmur indicates heart disease nor is it necessarily of cardiac origin This fact so often is lost sight of that it has seemed necessary to some to teach

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an altogether too extreme attitude of indifference toward the finding of a systolic murmur with no associated abnormalities Diastolic murmurs are most often organic while systolic murmurs are most often of functional origin

Organic murmurs that result from structural changes in the valve are most significant and are due to eddies produced by defects of organic or pathological scar tissue origin These are of the greatest significance and are to be recognized definitely and differentiated from inorganic or functional murmurs At times this differentiation is difficult The differential points will bear close study

Characteristics of organic murmurs aside from their time positions in the cardiac cycle are important and interesting and may contribute some to diagnosis and prognosis The duration of the murmur, and whether or not the heart sounds are replaced may be taken as criteria of the extent of a given lesion The quality, whether rasping harsh strident hissing whining blowing soft, low or high pitched loud or faint suggests to some extent the character of the pathological changes present and the condition of the heart muscle A change in the quality of any murmur is strongly suggestive of the presence of an active vegetative valvulitis or of a change in the muscle tone or response

Diastolic murmurs usually indicate the presence of chronic cardiac valvular disease and are only rarely functional as in the presence of extremely high intra aortic and intrapulmonary artery pressures The rare high pitched, evanescent, functional aortic diastolic murmur of hypertension is such an exception Another is the rare functional pulmonary high pitched diastolic murmur that is the result of dilation of the pulmonary artery and ring from the back pressure of mitral stenosis

Functional diastolic rumbles are found in patients with diffusely enlarged hearts in which the mitral ring is relatively small for the dilated ventricular cavity Such an explanation has been offered in several conditions In patients with severe chronic anemia as the sickle cell type with cardiac dilatation a low presystolic rumble with a loud third heart sound frequently is mistaken for a mitral stenosis rumble Congenitally patent ductus arteriosus may be present with such a rumble this will disappear when the patent ductus arteriosus has been closed The mitral stenosis combination of signs the rumble and P accentuation along with the continuous or machine murmur in the pulmonic area will indicate that mitral stenosis is not present

Functional late diastolic or presystolic low pitched murmurs at the apex in the presence of a loud third heart sound have been found in hypertensive patients with diffusely enlarged hearts with relatively narrowed mitral orifice and chronic left ventricular dilatation that at autopsy showed no organic valvulitis Christian and O Hare described such late crescendo murmurs in patients with chronic hyper tension and cardiac enlargement

The functional mitral Austin Flint rumble of relative obstruction at the mitral ring is encountered most commonly in the South where aortic insufficiency of syphilitic etiology is frequent The presence of signs of syphilitic aortitis with free aortic regurgitation would be definitely against the possibility of the presence of organic mitral stenosis in these patients An aortic regurgitant murmur in a young male who has no signs of aortitis even if he has no definite history of rheumatic fever points strongly towards the presence of an accompanying organic mitral stenosis when there is a clear cut diastolic rumble

The rumbling diastolic murmur usually indicates obstruction of an organic type in the mitral or tricuspid valve regions However besides the two functional diastolic rumbles just described there have been reported by St Lawrence and T Duckett Jones and Bland a goodly number of cases with transient rumbles in diastole Such presystolic murmurs were heard in 32 patients with acute rheumatic fever and were found to be absent in these patients eight years later The explanation offered was that these patients had acute rheumatic pancarditis with greatly dilated left ventricular cavities for which the normal sized mitral valve orifice was relatively small and thus functioned as a relative stenosis

Adhesive mediastinopericarditis fairly frequently has produced hypertrophy and dilatation of the heart particularly an enlarged left ventricle and may be accompanied by a rumbling apical diastolic murmur This rumble is considered by White and by others to be due to the greatly dilated left ventricular cavity for which again the normally sized mitral orifice was relatively small and therefore relatively stenotic Parietal anchorage of the pericardium may be suggested by fixation of the impulse and systolic retraction of the chest wall The heart with constrictive pericarditis usually is small rather quiet and free of murmurs

Wyckoff reported 3 most unusual cases of functional diastolic rumbles at the apex and found 7 more in the literature In these rumbling apical diastolic murmurs were heard during life but no organic mitral stenosis was demonstrable at autopsy Instead there were found sclerosis and dilatation of the pulmonary artery and apparently an obstruction of the lesser circulation There was enormous increase in size of the right ventricular muscle mass such that the interventricular septum actually bulged from the right into the left ventricle This bulge as Posselt had noted produces a stenosis of the entire left ventricular heart chamber In these cases there were present all of the signs of mitral stenosis with no history of rheumatism or any rheumatic infection and with no signs of pulmonary congestion or dilatation of the left atrium Wyckoff has pointed out that the presystolic crescendo element is absent in these pseudomitral stenosis murmurs

Complete left bundle branch block occasionally is responsible for a functional diastolic sound Asynchronous action usually results in a delay in the contraction

of the left ventricle This late contraction often produces a rumbling third sound in diastole that may be mistaken for the rumble of mitral stenosis It occurs, however in individuals past middle life who often also present a conspicuous double apex impulse Electrocardiograms will show the intraventricular conduction disturbance

Functional Systolic Murmurs —With the exception of the specific ones mentioned above functional murmurs are systolic in time and originate in the pulmonic mitral and tricuspid areas These murmurs although all classed as functional are actually of varying mechanism A relationship of various slight disturbances producing systolic murmurs is suggested by the use along with the term, functional of other more or less synonymous terms as relative myocardial hemic, physiological accidental exocardial extracardiac and cardiorespiratory Such designations have been used in the confusing terminology of these murmurs

Functional murmurs commonly are produced by compression with partial obstruction of the pulmonary artery or by a physiological insufficiency of a valve ring resulting from muscular relaxation Position and pressure changes in the precordial lingula of the lung and occasionally pericardial abnormalities give rise to sounds that must be differentiated from murmurs The determination of the origin of a given murmur though highly desirable often is difficult The murmurs of this group, it is evident are not due to a primary valvulitis but are due to secondary changes in the heart muscle and in the valvular rings Nutritional and anoxemic disturbances are the indirect effects of other more or less permanent cardiovascular changes Reduction of the tonus of the cardiac musculature results in ventricular dilatation and consequent stretching of the valve ring

The combination of a systolic murmur along with a diastolic in the same valvular area adds weight to the probability of the presence of true valvular damage On the other hand a systolic murmur alone must be associated with a history of rheumatic fever and other signs such as an accentuation of the pulmonic second sound, a shock a thrill or a plateau pulse before it can be considered evidence of an organic valvular defect

The position direction and distance of propagation or transmission of systolic murmurs and the effect upon them of respiration bodily posture exercise vagus stimulation or relaxation or of drugs as amyl nitrite atropin epinephrin and pilocarpin are all of some significance Very loud widely transmitted high pitched murmurs intensified by breathing exercise or drugs and present in all body postures are of organic origin

Apical systolic murmurs due to so called relative functional insufficiency make up a large proportion over 70 per cent as Christian has pointed out of what generally has been considered erroneously chronic mitral valvular disease The absolute differentiation of organic systolic functional murmurs on the basis of

physical characteristics usually is not possible Functional murmurs are accompanied not by the conspicuous accentuation of the pulmonic second sound but by an exaggerated tambour like aortic second sound A history of rheumatic fever is lacking but there is present hypertension anemia or some other similar etiological factor damaging the myocardium The functional murmur generally is poorly transmitted It may be heard moderately well over the precordium and toward the anterior axilla, but unlike the systolic murmur of organic valvular damage rarely is it conveyed to the posterior axilla or to the angle of the left scapula and the left interscapular region of the back

The mechanism of the production of functional atrioventricular systolic murmurs is purely hypothetical The closure of the atrioventricular valve is considered to be due in part to the contraction of the atrial muscle at its attachment to the ring and in part to the lifting of the valve leaflets in presystole The absence of the first factor in the atrial standstill in fibrillation is considered by Henderson and Johnson to be sufficient to account for the relative atrioventricular insufficiencies and the apical systolic murmurs so constantly found in atrial fibrillation

Treguboff considered hyperexcitability of the vagal fiber innervating the papillary muscles producing spastic contraction of these and increased tension of the chordae tendineae as the mechanism of relative valvular insufficiency This explanation seems rather far fetched as the explanation of the cause of inorganic apical systolic murmurs in neurasthenics with cardiac neuroses palpitation dyspnea and pain Treguboff maintains that with epinephrin the intensity of this type of functional murmurs is increased while under atropin the murmurs disappear Atropin does not influence organic systolic murmurs and therefore Treguboff also advocates its use as a differential diagnostic method

Left basal systolic murmurs found in the upper left second interspace are slightly rough in thin chested individuals but for the most part are soft blowing and insignificant Systolic murmurs sometimes erroneously spoken of as accidental in this pulmonic area of auscultatory romance when unaccompanied by thrills and other signs probably are due to the actual compression of the pulmonary artery Flatness or concavity of the chest often can be demonstrated to account for the murmurs Externally invisible causes of slight pressure on or of constriction of the conus arteriosus or pulmonary artery or pressure encroachments upon the conus or the artery are possible explanations The murmur evidently may result sometimes from the ejection of the blood through the firm spastic pulmonic valve ring into the more or less easily distended thin walled pulmonary artery

Cardiorespiratory murmurs soft and blowing and systolic in time usually are heard over the lower precordium and at the apex Changes in position and in the

air content of the lung as a rule, modify these murmurs Forced expiration especially may diminish them often to the point of inaudibility The usual explanation given is that the air by each systole of the heart is forced out of the lingula of the lung that overlies the heart in any individual with a deep inferior pulmonary incisura The French view is the opposite namely that with each systole of the heart there is a sort of vacuum created by the reduction of the heart s volume, and that air is drawn suddenly into the lingula, thus producing a suction like systolic murmur

Pericardial sounds at times may simulate closely the more or less harsh intra cardiac murmurs The pulmonic second sound as Warthin pointed out long ago, is distinctly accentuated as a result of pericardial tension changes exerted on the thin walled pulmonary artery just distal to the valve Pericardial friction sounds as a rule however, are of a distinctly scratchy character and last through a part or the whole of diastole as well as systole This is unusual for intracardiac mur murs which have a fixed relationship in the cardiac cycle The area of maximum intensity of pericardial friction sounds usually is over the midsternum to the left, i e just over the conus arteriosus, where the heart comes close to the wall The sound may be similar to that of the ordinary valvular lesions Pressure intensi fies the grating quality of the friction as does also the left lateral or knee chest position To and fro pericardial murmurs are unaccompanied by peripheral vascular phenomena

Vibration of the precordial structure resulting from an overactivity of the heart may produce a sound which through a lightly applied stethoscope simu lates closely a diastolic rumble This rumble occasionally is late in diastole and is often interpreted erroneously as the rumble of mitral stenosis Firm pressure with the stethoscope however will completely suppress or muffle this type of adventitious sound

The murmurs of organic valvular deformities which can be taken unequivo cally as reliable criteria of heart disease are for the most part diastolic in time Furthermore usually they are loud and clearly audible under varying conditions and in various positions over the apex or over the base of the heart and intensified by exercise and after forced and maintained expiration of air from the lungs

Specific Symptoms Cardinal Signs, Prognostic and Diagnostic Criteria and Differential Data of the Various Valvular Lesions

Mitral Insufficiency

Mitral insufficiency in a pure organic form unassociated with stenosis is a rare valvular lesion It may be present only as a very early manifestation of rheu

matic valvulitis Mitral insufficiency occurs most often in young individuals with rheumatic fever, but occasionally it persists as a dominant lesion in rheumatic mitral disease even into old age but practically always mitral stenosis of some degree also develops As a pure lesion it is less common than formerly it was thought to be and the diagnosis had best be made only in the presence of a diastolic apical rumble as well as the systolic murmur i e when mitral stenosis also is present

The reliable criteria for the diagnosis of organic mitral insufficiency are a history of rheumatic fever in one or another of its forms as a migratory arthritis chorea growing pains tonsillitis or erythema nodosum along with evidences of dilatation of the left atrium In elderly individuals atheromatous or calcareous degenerative disease may dominate the picture as the etiology of valvular pathology but frequently in the distant backgrounds there were rheumatic lesions

Symptoms are not pathognomonic Symptomatology may be vague Sometimes neuralgic pain and tenderness over the heart s apex impulse and along the left heart border may be complained of

The *cardinal sign of mitral insufficiency* consists of a rough loud apical systolic murmur which may replace the first heart sound in part or in toto A sharp first sound may persist This is transmitted to the left axilla and sometimes to the angle of the left scapula and into the left interscapular region Secondly there is accentuation of the pulmonary second sound Auscultatory data are not in themselves diagnostic but must be accompanied by signs of dilatation of the left atrium Percussion may reveal suggestive increase in the left parasternal dullness at the level of the second and third ribs and interspaces The left ventricular border also may be very slightly displaced to the left All of this is significant in the absence of hypertension other murmurs or evidences of myocardial insufficiency

Other methods of physical examination reveal nothing that is pathognomonic of organic mitral insufficiency On inspection there is rarely bulging of the chest wall diffuseness of the apex impulse and no conspicuous displacement of the apex to the left On palpation little if any precordial heave or systolic thrill or increased tension of the pulse is to be expected Percussion may not be reliable enough to be acceptable as evidence of the characteristic extension of the left atrial wall beyond its normal limit This may be demonstrated directly by the cardioroentgenfluoroscopist or by the roentgenologists in placing the patient in the right oblique position and fluoroscoping him during the swallowing of a thick barium sulfate paste In organic mitral insufficiency the dilatation of the left atrium causes the esophagus to be arched backward and to the right as is true also in mitral stenosis

The *differential diagnosis of organic mitral insufficiency* calls for considera

tion and ruling out of all of the other causes of apical systolic murmurs. The characteristics of an organic murmur in contrast to those of functional murmur as outlined above must be present. The systolic apical murmurs of cardiorespiratory origin, of relative mitral insufficiency, of tricuspid insufficiency, of septal defect and of aneurysm behind the heart which causes forceful precordial pulsation, must be differentiated.

The cardiorespiratory or exocardial murmurs usually disappear during expiration of air from the lingula of the left upper lobe of the lung which normally is anterior to the heart during inspiration. In emphysematous chests the continuously inflated lingula remains in front of the heart. This murmur can be heard better in patients that are lying down than in those who are sitting or standing up. It is not transmitted. Cardiorespiratory murmurs are soft and blowing. Pericardial sounds usually are not confined absolutely to the systolic cardiac cycle.

The murmur of relative mitral insufficiency is most difficult of differentiation. The relative incompetency arises as a temporary or persistent post infectious or anoxic relaxation or stretching of the mitral ring. It is blowing and soft but not well transmitted into the axilla; sometimes, however, it is loud and transmitted into the axilla. The presence of a serious infectious disease, severe chronic anemia, hypertension and cardiac enlargement are all in favor of murmurs being relative or functional rather than organic, particularly in the absence of a history of rheumatic fever.

The systolic murmur of tricuspid insufficiency presents its point of maximum intensity in the fourth interspace in the parasternal line. There is no accentuation of the pulmonic second sound. It is not transmitted to the axilla and usually it is accompanied by a positive venous pulse in the neck veins and in the liver.

A defective interventricular septum produced by congenital aplasia of the pars membranacea or the result of an acquired septal infarction and necrosis, gives rise to a loud, often rough systolic murmur that is maximal beneath the sternum opposite the third interspace, transmitted slightly to the right and usually accompanied by a systolic thrill. A thrill is rarely demonstrable in mitral insufficiency and certainly never in the mid or upper sternal region. Basal systolic murmurs need not be considered in the differential diagnosis of mitral insufficiency. If the exacting diagnostic criteria are adhered to, the diagnosis of organic mitral insufficiency will be infrequent since the condition is most uncommon.

In cases meeting the rigid requirements the *prognosis* is by no means as good as is generally suspected. It is poorly borne or poorly compensated for relatively early and irreparable dilatation may be expected. The rheumatic mitral valvulitis with very predominant insufficiency is very prone to fatal subacute bacterial endocarditis.

Mitral Stenosis

Mitral stenosis is the commonest chronic cardiac valvular lesion found in the heart clinics of the North Usually it is associated with some degree of mitral insufficiency The relative rarity with which the lesion is recognized in the South is not an absolute index of its frequency In itself mitral stenosis is diagnostic of rheumatic heart disease Among the reliable criteria one must include the history of rheumatic fever in one form or another at least six months and usually a few years previously However a positive history is obtainable in only about half of the cases Mitral stenosis usually is fully developed in early adult life and only exceptional cases live beyond the fiftieth year

Symptoms may not be recognized for years but as a rule the patient with mitral disease and especially stenosis of any grade notes palpitation and breathlessness early in contrast to the patient with aortic disease Symptoms are not pathognomonic but consciousness of heart action shortness of breath occasionally dysphagia hoarseness cough and hemoptyses in a fever free woman are suggestive of the presence of mitral stenosis Cardiac precordial aching and angina pectoris may be complained of

The *cardinal signs of mitral stenosis* are revealed by auscultation There is a sharply localized low pitched rumbling rough slowly vibratory early middle or late diastolic often crescendo murmur heard directly over or above and slightly to the right of the apex impulse This murmur is heard best with the patient in the left lateral position A loudly accentuated pulmonic second sound with the apical rumble may be considered practically pathognomonic of mitral stenosis The presence of gallop rhythm a loud third heart sound reduplication of second sound and a blowing systolic murmur are common accompaniments

Percussion should bring out suggestive high left parasternal dullness as evidence of dilatation or increased distention to the left in the region of the atrium

Palpation usually reveals a sharply localized rather short rough vibration thrill during diastole and a sharp systolic shock over the circumscribed apex impulse inside the nipple line and a diastolic shock over the pulmonic area Both are almost pathognomonic signs in themselves The thrill may be only presystolic occasionally mid and late diastolic in rare cases almost toto diastolic Overactivity of the hypertrophied dilated right atrium and the conus arteriosus may be felt to the left and over the mid precordium The pulse is characteristically small The pulse rate and rhythm become irregular because of the intervention of auricular fibrillation

Inspection reveals corroborative evidence both generally and locally The characteristic mitral facies consist of the purplish roughed lips and the slightly

cyanotic high, malar flush The precordium may be slightly bulging Fluoroscopic observation is the most valuable diagnostic procedure Often it will reveal characteristics bulging of the left atrium and in the right oblique position arched backward displacement of the esophagus The finding of calcification in the mitral valve also is confirmatory evidence of rheumatic mitral disease

The *differential diagnosis of mitral stenosis* demands a careful consideration of the few conditions that are accompanied by rumbling, apical, diastolic murmurs heard best inside over or occasionally directly above the apex impulse with the patient lying in the left lateral position A rumbling, pseudopresystolic sound that may be confused with the crescendo element of a mitral stenosis murmur may be found in hyperthyroidism and in neurocirculatory asthenia in the presence of overactivity of the heart This sound originates in the vibration of the precordial structures and is heard only on light pressure auscultation Firm pressure of the stethoscope to the chest wall erases most of the functional, diastolic sound and thus aids in the differential diagnosis by muffling vibrations of the chest wall

Functional diastolic rumbles are relatively rare but do occur in patients with dilated left ventricle from various causes and are to be differentiated as described above In elderly subjects with bundle branch block the asynchronous action of the ventricles may give rise to a split first heart sound that may be easily mistaken for the rumble of mitral stenosis The other occasional functional diastolic rumbles have been described in detail under the heading of functional murmurs

Tricuspid stenosis may give rise to a similar rumble, but almost invariably it is found in patients who also have mitral stenosis The tricuspid rumble usually is localized nearer the sternum and the xiphoid process the mitral rumble The pulmonic second sound is not accentuated in a pure tricuspid lesion but actually is diminished and a systolic murmur practically always accompanies it as pure tricuspid stenosis is most rare Engorgement of the right atrium may be percussed out to the right of the sternum and outlined with the teleroentgenogram or orthodiagram The neck veins and the liver may be engorged and show prominent A and V waves in a phlebogram and the patient shows an icteric cyanosis It is to be remembered that pure tricuspid stenosis is exceedingly rare The signs usually accompanying mitral stenosis and aortic stenosis are confusing

Congenital heart lesions occasionally give rise to diastolic murmurs These murmurs usually are of higher pitch In some cases of a persistent ductus arteriosus a diastolic rumble is heard at the apex This must not be considered to indicate mitral stenosis when there are signs of a persistent patency of the ductus arteriosus At the same time it is to be remembered that patients with congenital heart disease frequently suffer from a superimposed rheumatic carditis

Various *stages of mitral stenosis* may be distinguished roughly by signs which

indicate increasing obstruction and consequently more serious prognosis The stages have been designated commonly as 1, 2, 3 and 4 with 2 and 3 overlapping

In stage one of mitral stenosis with obstruction of slight grade there is a short late diastolic rumble, but the mitral first sound has become snapping and the second sound persists at the apex There is some accentuation of the second sound in the pulmonic area The aortic second sound also is present The left atrium has enlarged some encroaching somewhat upon the retrocardiac space, *but it does not reach the vertebral column the expert fluoroscopist will be able* to demonstrate the left atrial dilatation No enlargement of the heart is detectable by the teleroentgenogram The electrocardiogram is not definitely abnormal though the P waves may be slightly exaggerated The cardiac or reserve exercise tolerance usually is good and pregnancy and infections are well borne in this stage

In the second or moderately advanced stage the obstruction has increased considerably and these changes are reflected in the changes in the physical signs There can be heard now an opening snap due to vibration of the mitral leaflets a higher pitched early mid and late diastolic rumbling and a sharper louder more snapping mitral first sound There is a falling off of the left ventricular output to the point of an almost complete disappearance of the aortic second sound as a result of the reduced aortic tension and a consequent dropping out of the mitral second sound The left atrium fills the retrocardiac space to the bodies of the vertebrae The left atrial enlargement can be demonstrated roentgenographically and hypertrophy of the right heart begins to give more evidence of its presence electrocardiographically

In the third or advanced stages the rumbling diastolic murmur has become higher pitched and longer filling most of diastole diminishing in mid diastole only to increase in intensity late in diastole with a whirlwind crescendo ending in a sharp mule kick first sound at the apex The extreme snapping character of the first sound has been attributed to the contraction of the left ventricle on a reduced volume of blood or to the sharp closure of the tricuspid leaflets caused by the increased pressure The second sound in the aortic area and in the mitral area may not be audible The pulmonic second sound is reduplicated The left atrium increases to its maximum in size and may compress the esophagus and even extend to the right beyond the right atrial border The heart thus increases in transverse diameter The electrocardiogram shows right ventricular predominance and the large P waves of atrial hypertrophy The rhythm eventually becomes absolutely irregular as atrial fibrillation is precipitated and with this the presystolic accentuation of the rumble becomes less conspicuous

In the final stage dilatation may *become extreme and the* signs even to the diastolic rumble may be decreased considerably Sometimes no murmur is

heard when the valve orifice is very small. The right ventricle fails, and the tricuspid safety valve effect may develop with the systolic murmurs of mitral and tricuspid regurgitation and the positive jugular and liver pulsations becoming prominent.

Prognosis depends to some extent on the grade of stenosis. Concomitant regurgitation does not improve the outlook. The presence of atrial fibrillation adds somewhat to the seriousness of the disease since the development of auricular mural thrombi is facilitated. The presence of an elevated systemic blood pressure makes the prognosis more favorable. A combination of slight aortic disease seems to make mitral stenosis better tolerated. An occasional patient may suffer cerebral embolism from an early, formed, dilated atrial thrombus and live many years, helped some perhaps by a hemiplegia. As a rule, however, embolism is an ill omen, and death usually follows within five years according to the studies of Levine and Harris. The funnel shaped fused mitral valve leaflets with the buttonhole slit or fish mouth orifice often become calcified but rarely are vegetations of subacute bacterial endocarditis likely to become attached to the smooth mitral diaphragm.

Aortic Regurgitation

Aortic regurgitation is the earliest reliable indication of aortic valvulitis of rheumatic or infectious origin and also the first reliable sign of syphilitic aortitis. In rare instances congenital aortic dextroposition or a bicuspid valve may be the basis for aortic insufficiency. Aortic incompetency is the most common and, when fully developed, the most regularly recognized valvular defect occurring in the South. Syphilitic aortic disease usually is isolated except frequently, however, with a relative mitral insufficiency. Rheumatic aortic valvulitis practically always is associated with organic mitral and sometimes with organic tricuspid disease.

Dilatation of the aortic root and valve ring with spreading of the commissures and thickening and retraction of the aortic cusps are slowly progressive processes which gradually increase the interference with valvular competency. Blood flows back into the left ventricle in diastole at the same time that the ventricle fills from the left atrium. The added volume of blood causes dilatation which in turn is the stimulus to hypertrophy.

In the early stages symptoms usually are absent and may not appear for years. Signs of slight degree of aortic valvular incompetency may be elicited only after special maneuvers. As the degree of insufficiency increases the pulse pressure widens and conspicuous peripheral phenomena develop and give rise to more striking signs and symptoms. These are the result of the alterations in the dynamics of the circulation that accompany incompetency of the aortic valve.

A patient with aortic regurgitation presents no absolutely specific or pathognomonic *symptoms*. A burning sensation under the manubrium brought on by exertion or emotional stress suggests syphilitic aortitis. There are a few other somewhat characteristic or at any rate strongly suggestive symptoms that accompany higher grades of aortic valvular defect. Hypersensitive patients with moderately free aortic regurgitation suffer often from palpitation and sometimes complain of a throbbing sensation throughout the body on exertion. It is not at all uncommon for these patients to suffer with high substernal burning distress and cardiac pain. Sometimes the sudden rapid rise to the upright position brings on giddiness, vertigo, faintness and often headache. The cerebral circulation may be so interfered with that it causes disturbances in memory, hallucinations of vision, of hearing and sometimes of smell. Paroxysmal attacks of dyspnea, cough and frothy blood tinged exudate of pulmonary congestion and edema are not uncommon as evidence of left ventricular failure.

The cardinal sign of aortic regurgitation is the high pitched, often musical aortic diastolic murmur that usually is heard in the aortic area in the second right intercostal space near the sternum. The murmur frequently is heard better in the third left intercostal space, the so called secondary aortic area, and along the left border of the sternum. It is propagated over the precordium to the apex of the heart or to the left axilla, changed or unchanged in character. In the absence of the aortic second sound there is a relative increase in the pulmonic second sound. The diastolic blood pressure practically always is lowered and the systolic often is elevated, thus increasing the pulse pressure. The aortic diastolic murmur transmitted unchanged to the apex and to the axilla, as described by Belthazar Foster, may be considered to be the result of regurgitation through the anterior segment of the aortic valve. The aortic diastolic murmur that is changed to an Austin Flint rumble at the apex may be the result of backflow through the posterior segment of the aortic valve. The cooing or sawing murmur of Hodgkin Key is due to buckling downward of the right anterior cusp with or without involvement of the posterior aortic cusp.

The secondary peripheral phenomena of aortic regurgitation depend upon the elevation of the pulse pressure. This accounts for the throbbing of the carotids and subclavians and of the peripheral arteries, arterioles and capillaries. The high pulse pressure drive into the capillary bed produces the capillary pulsation visible in the nail beds, in the lips compressed under glass or in the skin of the forehead made hyperemic by friction. Auscultation over the femoral or brachial artery with slight compression by the bell of the stethoscope often reveals the characteristic pistol shot sound, the double sound of Traube and the diastolic murmur of Duroziez.

Additional suggestive signs are revealed on close inspection of well developed

cases of aortic regurgitation The aortic facies with systolic momentary flushing alternating with diastolic blanching is present in extreme cases Pallor with a slight yellowish tinge of the skin suggests that the lesion may be of syphilitic aortitis origin, while pallor with a grayish cast suggests rheumatic aortic valvulitis The cafe au lait color appears in the presence of a complicating subacute bacterial endocarditis The movement of the ear lobes and the nodding of the head with each systole are seen only rarely Throbbing of the neck vessels, which first attracted Corrigan s attention, is seen fairly commonly in free aortic regurgitation

The cardiac apex usually is displaced downward and to the left but this evidence of cardiac enlargement occasionally may not be present Palpation confirms the presence of a strong persistently heaving apex impulse which usually is visible as well as palpable when left ventricular enlargement has developed An aortic diastolic thrill very rarely is present The quick, water hammer, the classical altus et celer pulse is accentuated usually quite strikingly, on raising the arm One may outline increased retromanubrial dullness in cases of syphilitic aortitis The area of increased cardiac dullness to the left is in itself not of pathognomonic shape

The *differential diagnosis of aortic regurgitation* calls for consideration of such conditions as hyperthyroidism and anemia which may display a collapsing pulse and capillary pulsation but no aortic diastolic murmur The presence of the peripheral vascular phenomena described above clearly characterize the aortic lesions but they are not always conspicuous, especially in rheumatic aortic regurgitation

Relative pulmonary insufficiency that accompanies high grade mitral stenosis gives rise to the high pitched diastolic Graham Steell murmur heard to the left of the sternum However this syndrome presents no vascular signs in the periphery On fluoroscopic examination in patients with pulmonary regurgitation there is usually a throbbing of the bronchovascular tree with so called dancing hilar shadows

The accompanying diastolic rumbling at the apex usually is most conspicuous, and all the characteristics described above as the most reliable signs of mitral stenosis are present A history of rheumatic fever favors the diagnosis of mitral stenosis and a relative pulmonary insufficiency though rheumatic aortic valvulitis with insufficiency may be present Rheumatic mitral disease is practically always present in those with rheumatic aortic disease A negative rheumatic fever history a positive venereal history and positive serology of course favor the lesion being that of syphilitic aortitis with dilatation of the aortic ring

The presence of a high grade hypertension sometimes will dilate the root of the aorta and produce a diastolic murmur A congenitally bicuspid aortic valve is more likely to permit regurgitation under increased aortic pressure In these

conditions accompanying aortic systolic murmurs are common because of the concomitant aortic dilatation beyond the ring Congenital aortic defect with dextrorotation of the aorta must be considered occasionally as possible cause for a high pitched basal diastolic murmur Differentiation usually is not difficult because of the presence of other signs of congenital heart disease as cyanosis and thrills usually with evidence of right ventricular preponderance The peripheral phenomena are not in themselves diagnostic of aortic regurgitation as they may develop completely in a patient with a congenital arteriovenous shunt or an acquired communication as a syphilitic or mycotic fistula at the root of the aorta from a sinus of Valsalva into the pulmonary artery the right atrium or the vena cava There are thrills and continuous systolic and diastolic machine like murmurs demonstrable over any arteriovenous communication The fairly common persistent patency of the ductus arteriosus presents these in the pulmonic area i e in the second left intercostal space

The *prognosis of aortic valvular incompetency* depends on a good many factors Among these factors the etiology the extent of the anatomical lesion the effect on the coronary circulation and the status of the myocardium are important A slight defect may be present for years without being brought to the attention of the physician because of lack of symptoms It is not at all uncommon to have the characteristic diastolic murmur recognized quite accidentally during a routine examination for insurance or for athletic work I have found evidence *of aortic insufficiency in first rate athletes even in a star end of a prominent university* football team Such lesions usually are of rheumatic origin Rare cases of syphilitic aortic regurgitation go for years without visible progression

The higher the pulse pressure and the lower the diastolic pressure the less satisfactory the outlook due to the fact that the adequate irrigation of the coronary system depends in a large measure on the diastolic pressure The functional efficiency of the anterior sinuses of Valsalva and the anterior aortic cusps must be taken into consideration It is quite likely also that the prognosis is less favorable when due to anatomical changes that are most extensive in the anterior cusps Such would render less effective the deflection of blood from the cusps into the orifices of the two coronary arteries When the primary involvement is localized in the posterior cusp and regurgitation is through the posterior sector the coronary irrigation is less affected

After myocardial insufficiency has once intervened particularly in a patient with aortic regurgitation and particularly in one whose involvement is in the anterior cusp the chances of complete reestablishment of circulatory equilibrium are poor

The onset of heart failure or myocardial insufficiency frequently is very sudden in patients with syphilitic aortitis who present aortic regurgitation The

sudden rupture or the more gradual turning over of a damaged, right anterior, aortic cusp or the presence of any other pathological process, that would tend to embarrass more or less promptly the coronary circulation, would serve to precipitate congestive failure The presence of cardiac pain or anginal symptoms associated or not with acute physical strain in a patient with aortic regurgitation forbodes imminent dissolution

Rheumatic aortic disease is tolerated better as a rule than is syphilitic aortitis with aortic insufficiency The gradual development of rheumatic aortic stenosis adds further burden and usually makes the prognosis more serious in the adolescent In those that survive however beyond fifty years the development of calcareous disease seemingly has decreased the grade of regurgitation and thus improved the coronary circulation Aortic regurgitation sometimes seems to improve and make better tolerated high grade mitral stenosis Tricuspid insufficiency and stenosis added to the aortic and mitral disease, usually serve only to shorten life These patients probably go into heart failure sooner but frequently they live longer, as much as a decade, in congestive failure of a moderate grade Multivalvular lesions sometimes seem to be borne better than single lesions, but only apparently is this the case as the span of years is shortened as a rule

Aortic Stenosis

Aortic stenosis is a more common lesion than it was formerly thought to be It should be recognized more frequently as it makes up a third of rheumatic valvular lesions It is serious when it occurs in younger individuals who have chronic rheumatic aortic disease It is found often as a calcified lesion in the aged individuals in whom it had not been suspected during life Christian directed attention to its frequency and easy recognition He pointed out that its presence should be recognized easily by the roentgenologist, which soon proved to be the case In general aortic stenosis is very well tolerated and asymptomatic in most cases

Symptoms occasionally develop in those with very high grade aortic obstruction in whom the blood pressure and the pulse pressure are so low as to interfere with cerebral and coronary circulation These patients may complain of headaches weakness faintness vertigo and occasionally syncope On the other hand they may experience such cardiac symptoms as palpitation of a slow forceful type with precordial aching and anginal failure Myocardial insufficiency begins to develop after ventricular failure and there is often dyspnea cough and pulmonary edema followed by right ventricular failure congestion in the viscera and edema

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The characteristic collapsing pulse is felt in the carotids and in the brachials and radial arteries when as often is the case considerable regurgitation coexists A regular slow small double humped and flat topped pulse with slow notched rise sustained summit and slow fall has been recognized for many years as diagnostic of aortic stenosis and designated as pulsus rarus parvus anacroticus et bisferiens and the plateau pulse Percussion may reveal no abnormal retromanubrial dullness but an increase in the cardiac dullness to the left with the *characteristic en sabot wooden shoe shaped outline demonstrable usually in* the roentgenographic study The carotid and subclavian arteries usually are not pulsating visibly The apex impulse is displaced downward and outward and presents a steady heave in systole The blood pressure usually is low and the pulse pressure is most significantly low

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Aortic stenosis in patients who have lived beyond adolescence and in whom active rheumatic fever has subsided seems to have a fairly good *prognosis* Decades may pass after the lesion has been discovered and the patient remains

sudden rupture or the more gradual turning over of a damaged, right anterior, aortic cusp or the presence of any other pathological process, that would tend to embarrass more or less promptly the coronary circulation, would serve to precipitate congestive failure The presence of cardiac pain or anginal symptoms associated or not with acute physical strain in a patient with aortic regurgitation forbodes imminent dissolution

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of the portal system Cyanosis and jaundice combine to produce a peculiar olive coloring in the skin of the patient The development of abdominal ascites supersedes the development of edema of the extremities

The *cardinal signs of tricuspid insufficiency* consist of a peculiar mixed cyanotic, icteric skin discoloration conspicuous engorgement and pulsation of the deep jugular neck veins with a single positive venous pulse of the ventricular form with a single large V wave in the phlebogram and an expansile positive systolic pulsation of the liver which may be seen on inspection and confirmed by hepatogram The expected harsh loud grating systolic tricuspid murmur localized over the lower left sternum near the xiphoid and transmitted toward the right may be faint distant or absent in a very free regurgitation The pulmonic second sound would be decreased if the lesion were a pure one but again this is rarely the case as mitral disease commonly accompanies tricuspid disease The apex impulse is very diffuse and often there is retraction of the precordium over the right ventricle which sometimes may be seen and interpreted erroneously as a Broadbent s sign

On percussion dullness extending abnormally beyond the right border of the lower sternum is the result of distention to the right of the atrium rather than of hypertrophy of the right ventricle There are no signs of congestion or edema of the lungs The area of the hepatic dullness is enlarged and shifting dullness of ascites may be found in the abdomen Roentgenograms confirm the presence of enlargement of the heart s outline to the right with displacement of the esophagus to the left and engorgement of the great veins Kymographic records show decreased pulsations of the aorta along with increased amplitude of the left cardiac border which is made up of the right ventricle in these cases The electrocardiogram shows notched P waves and usually right ventricular preponderance The venous pressure is chronically elevated and the circulation time through the pulmonary system is definitely slowed

The *differential diagnosis of tricuspid insufficiency* calls for ruling out of transient relative safety valve dilatation of the tricuspid ring this is not always possible Other conditions that give rise to systolic murmurs in the tricuspid area along the left border of the sternum from the xiphoid to the third left intercostal space should be taken into consideration An anterior mitral leaflet insufficiency with shortened fibrosed chorda tendineae or subaortic narrowing may give a systolic murmur in the lower left sternal border region but usually at a higher level than that of the tricuspid systolic murmur The murmur of Roger of pure interventricular septal defect usually is accompanied by a thrill is heard slightly higher up in the third left intercostal space and presents no prominent neck veins right atrial or liver engorgement or expansile pulsation as are seen in tricuspid regurgitation

quite comfortable except for an occasional slight, increased disturbance in the circulation of the brain resulting in dizziness It is not at all uncommon to see aortic stenosis cases who have gotten along well into the fifth and sixth and even the seventh decades The strong thick walled, left ventricle hypertrophies to overcome the aortic obstruction much better than does the left atrium to compensate for mitral stenosis

In aortic stenosis as in regurgitation the status of the coronary orifices and the position and efficiency of the cusps behind which they originate determine largely the outlook since the coronary flow is most important If cardiac pain has developed and the coronary circulation has been interfered with, the prognosis is not good and sudden death may occur The carotid sinus reflex often seems to be hyperactive, syncopal attacks are not at all uncommon This may be in part a reflex from the ventricles The appearance of signs of left ventricular failure makes the prognosis less favorable After the intervention of such complications there is hope usually for only a few months or at the most, a few years, of life If tricuspid stenosis is present also, congestive failure may appear early and be tolerated for a good many years even as much as a decade Mitral stenosis is a usual accompanying lesion and does not alter the prognosis very much but it may decrease distinctly the outlook if the mitral and aortic valves are strikingly involved and both with stenosis

Tricuspid Insufficiency

Tricuspid insufficiency due to organic structural involvement of the tricuspid valve rarely is pure and isolated, but with some slight degree of stenosis and with mitral and aortic disease it occurs much more frequently than it is recognized It has been found in 25 to 30 per cent of all cases of chronic rheumatic mitral valvular disease Of these about two thirds had only slight damage with the resulting tricuspid insufficiency Almost 10 per cent presented sufficient narrowing to a circumference of less than 8 cm which would warrant the diagnosis of tricuspid stenosis There are two groups of patients affected by tricuspid disease A young group may present symptoms and signs almost indistinguishable from those of active rheumatic valvulitis and die of a pancarditis and panvalvulitis before the age of 20 A second group of patients who had milder episodes of rheumatic fever and who had relatively few symptoms and no acute congestive failure survive for another decade or two longer

Symptoms may be suggestive early as a feeling of tenseness and fullness in the neck and in the right upper quadrant These symptoms are the result of engorgement of the neck veins and of the liver Digestive disturbances as anorexia nausea a sense of fullness eructation and vomiting may result from congestion

olive discoloration of the skin, especially of the face is due to a combination of cyanosis and icterus

Chronic engorgement and presystolic and systolic pulsation of the deep jugular neck veins and expansile pulsation of the liver with chronic elevation of the venous pressure and prolongation of circulation time through the right side of the heart are the most pathognomonic signs There are usually other phenomena accompanying these signs because of the usual association of tricuspid regurgitation which places the whole venous blood column in communication with the right ventricle backward movement of the blood during ventricular systole is reflected as the positive expansile venous pulse in the neck and liver in addition to the presystolic waves In addition there usually are signs of mitral stenosis and insufficiency and very frequently those of aortic rheumatic disease The characteristic tricuspid type of chronic congestive failure consists of enlargement of the liver with or without pulsation and ascites developing in advance of edema of the lower extremities

In *differential diagnosis* a functional tricuspid rumble from the relative tricuspid stenosis that may occasionally accompany a functional Graham Steell murmur cannot be ruled out absolutely Mitral stenosis presents its rumble directly over the apex impulse and this with the pulmonic second sound accentuation is almost diagnostic Constrictive mediastinopericarditis usually produces engorged neck veins and liver with ascites but rarely the murmurs significant of tricuspid stenosis

Tricuspid stenosis likewise has a better *prognosis* clinically than one would expect theoretically Rare is it that the grade of stenosis approaches that of mitral stenosis The equal increase in right and left atrial pressures seems to postpone the onset of atrial fibrillation Some patients have gone through pregnancies without acute failure but usually the victims live only into their thirtieth year Tricuspid congestive failure is a most chronic type and patients have been followed as long as ten years after the intervention of ascites and edema An accompanying aortic stenosis seems to give the patient a longer life span by a decade and a half over that of the patients with pure tricuspid disease

Pulmonic Regurgitation

Anatomical or structural changes occur least often in the cusps of the pulmonic valve The pulmonic valve is singled out most rarely by an inflammatory process and damaged without involvement of several other valves In most cases of rheumatic fever a layer of fibrous tissue is laid down at the root of the artery following each episode of the disease Only rarely however is there penetration of the process with actual organic pulmonic valvulitis which on healing will result

The *prognosis of tricuspid insufficiency* generally is considered to be poor primarily because the chamber of the right atrium is dilated and the valvular actions of the orifices of the vena cava are most inadequate The blood mass is forced back into the great venous channels in the liver and into the neck veins It is surprising however, to find patients with pure tricuspid regurgitation of organic nature sometimes surviving a decade or more after symptoms and signs have been recognized

The safety valve action of the tricuspid valve, the development of a relative insufficiency frequently is accompanied by a sharp temporary relief in dyspnea as the result of the reduction in pulmonary congestion The chronically orthopneic patient suddenly finds himself able to recline in comfort for a while, but this is a false relief Congestion and pulsation of neck veins and liver soon develop and produce a sense of fullness and soreness

Tricuspid Stenosis

Tricuspid stenosis is found as an isolated lesion relatively rarely Only about 15 cases of pure tricuspid stenosis in the 250 reported cases of tricuspid valvulitis have been recorded About 10 per cent of all cases of mitral stenosis have some degree of tricuspid stenosis One third of these show marked stenosis one third moderate stenosis and one third slight stenosis In addition to this among the cases of rheumatic mitral disease almost 20 per cent more show some evidence of structural organic tricuspid disease resulting in tricuspid insufficiency with only a slight degree of stenosis The tricuspid leaflets in their cocked hat shape apparently are not as prone to fusion as are the mitral leaflets in their mitre shape, and the development of fish mouth narrowing rarely is found to be as marked as it is in mitral disease

Symptoms of note or of significance that could be considered to be in anyway pathognomonic are missing Palpitation with undue cyanosis on exertion may be present for years Some patients experience a sense of fullness in the chest, neck and in the liver region that they become aware of rather late as a rule Abdominal pain may be complained of as a result of engorgement of the liver of extreme grade with stretching of the overlying peritoneum

The *cardinal signs of tricuspid stenosis* are a rumbling mid diastolic murmur at the xiphoid near the lower end of the sternum transmitted very little toward the right, even very little to the right of the sternum a snapping first sound usually present in the same region over the right ventricle a pulmonic second sound decreased in intensity and absent signs of congestion and exudation in the lungs A late diastolic thrill may be palpable Increased dullness to the right of the sternum is evidence of a dilated right atrium The peculiar bluish green,

menger s syndrome usually is accompanied by greater right ventricular enlarge ment and dextroposition of the aorta which will give complicating peripheral vascular signs

The *prognosis* is not very well established in general probably it is as good as that of other valvular lesions if it is an isolated lesion If a complete cusp is destroyed the right ventricle may not bear up under the extra burden and com pensation may be inadequate When it is combined with tricuspid lesions it may make the latter more easily borne Some degree of stenosis usually is present also particularly when rheumatic fever is the etiology It is often a part of the quadrivalvular syndrome in the presence of which the patient usually does not survive beyond the third decade

Pulmonic Stenosis

Pulmonic stenosis although most common among congenital defects is most rare as an acquired lesion As an acquired lesion it is usually present when all four valves are involved which occurs quite infrequently but it has been recog nized clinically and proven by postmortem examination Rheumatic fever is the most likely cause Syphilis and arteriosclerosis rarely are localized in this region Acute infectious diseases may make congenital lesions clinically mani fest Congenital pulmonic stenosis in some instances may have been the result of fetal endocarditis

Symptoms rarely are characteristic rather late in developing and depend upon the grade of obstruction Shortness of breath may be an early manifesta tion usually the result of an obstruction to adequate pulmonary circulation and may be proportionately greater than other signs of heart failure A compensatory polycythemia and plethora develop These sometimes make the patient com plain of a sensation of fullness in the vascular bed

The *cardinal physical diagnostic signs of pulmonic stenosis* are a rough sys tolic thrill a loud rough systolic murmur to the left of the sternum with a decrease in the pulmonic second sound There are no changes in the carotid or peripheral pulses There is often a scratchiness over the tricuspid area and up into the pulmonic area as a result of overactivity of the conus arteriosus On palpation one discovers the characteristic rough systolic thrill in the pulmonic area and abnormal pulsations may be felt in the second and third intercostal spaces Percussion may reveal practically no changes Careful inspection will show some cyanosis in all cases This becomes more conspicuous as the grade of the obstruction develops and the polycythemia increases Clubbing of the fingers is a common sign There is no change in the peripheral systemic pressure or pulse pressure or in the form of the pulse wave

in subsequent distortion and incompetency Dilatation of the pulmonary root and secondary valvulitis may accompany some conditions as patent ductus arteriosus, the rare defective atrial septum and Eisenmenger s syndrome

Symptoms that might be considered characteristic have not been recorded Palpitation is felt often over the right ventricle, pulmonary conus and in the pulmonary area Breathlessness may be most prominent Retromanubrial distress, epistaxis hemoptysis and pain in the chest may occur in cases of acute verrucous endocarditis of the pulmonic valve

The *cardinal physical diagnostic sign* consists of the high pitched, musical diastolic murmur heard to the left of the sternum in the second left interspace propagated along the left sternal border toward the region of the xiphoid process This is accompanied by a decrease or an absence of the pulmonic second sound Occasionally there may develop a functional diastolic rumble over the tricuspid area similar to the Austin Flint murmur over the apex impulse in aortic regurgitation There are usually changes in other valvular areas as a result of accompanying lesions Peripheral vascular phenomena are significantly absent In arteriosclerosis of the pulmonary artery clubbed fingers may develop but are uncommon in acquired pulmonic lesions

Inspection may reveal abnormal pulsations over an overactive conus On fluoroscopic examination one may see dilatation of the right atrium and a widely pulsating pulmonary artery The expansile pulsation is transmitted into the bronchovascular tree producing a dancing of the hilar shadow On palpation one feels usually only the diffusely weak cardiac impulse at the apex and some pulsation in the second and third left intercostal spaces Percussion may reveal slight increase in the dullness of the third left interspace This is rarely demonstrable Sometimes the dullness extends to the right of the sternum The electrocardiogram may show the development of some right axis deviation

The *differential diagnosis of pulmonic regurgitation* calls for consideration of all of the causes of diastolic high pitched basal murmurs and particularly that of aortic regurgitation which often is heard best in the second and left third interspace i e in the so called secondary aortic area One must try to establish or rule out by the presence of the diagnostic criteria the possibility of a Graham Steell murmur of relative insufficiency that accompanies high grade mitral stenosis A history of rheumatic fever a relatively high diastolic blood pressure low pulse pressure the absence of arterial throbbing, right axis deviation in the electrocardiogram and abnormal P waves and prolonged PR interval are suggestive of rheumatic mitral stenosis and relative pulmonary insufficiency A history of syphilis and the presence of peripheral vascular phenomena and high pulse pressure throbbing of the neck vessels and water hammer pulse are in favor of the diagnosis of aortic insufficiency The pulmonic insufficiency of Eisen

menger's syndrome usually is accompanied by greater right ventricular enlargement and dextroposition of the aorta which will give complicating peripheral vascular signs

The *prognosis* is not very well established in general probably it is as good as that of other valvular lesions if it is an isolated lesion If a complete cusp is destroyed the right ventricle may not bear up under the extra burden and compensation may be inadequate When it is combined with tricuspid lesions it may make the latter more easily borne Some degree of stenosis usually is present also particularly when rheumatic fever is the etiology It is often a part of the quadrivalvular syndrome in the presence of which the patient usually does not survive beyond the third decade

Pulmonic Stenosis

Pulmonic stenosis although most common among congenital defects is most rare as an acquired lesion As an acquired lesion it is usually present when all four valves are involved which occurs quite infrequently but it has been recognized clinically and proven by postmortem examination Rheumatic fever is the most likely cause Syphilis and arteriosclerosis rarely are localized in this region Acute infectious diseases may make congenital lesions clinically manifest Congenital pulmonic stenosis in some instances may have been the result of fetal endocarditis

Symptoms rarely are characteristic rather late in developing and depend upon the grade of obstruction Shortness of breath may be an early manifestation usually the result of an obstruction to adequate pulmonary circulation and may be proportionately greater than other signs of heart failure A compensatory polycythemia and plethora develop These sometimes make the patient complain of a sensation of fullness in the vascular bed

The *cardinal physical diagnostic signs of pulmonic stenosis* are a rough systolic thrill a loud rough systolic murmur to the left of the sternum with a decrease in the pulmonic second sound There are no changes in the carotid or peripheral pulses There is often a scratchiness over the tricuspid area and up into the pulmonic area as a result of overactivity of the conus arteriosus On palpation one discovers the characteristic rough systolic thrill in the pulmonic area and abnormal pulsations may be felt in the second and third intercostal spaces Percussion may reveal practically no changes Careful inspection will show some cyanosis in all cases This becomes more conspicuous as the grade of the obstruction develops and the polycythemia increases Clubbing of the fingers is a common sign There is no change in the peripheral systemic pressure or pulse pressure or in the form of the pulse wave

The *differential diagnosis of pulmonic stenosis* of slight degree is most difficult and uncertain. The congenital type is easily recognized as it is usually of high grade. A systolic murmur in the pulmonic area of auscultatory romance is found very commonly in normal individuals. It probably should be disregarded entirely, unless it is accompanied by a very definite systolic thrill. There are such conditions as aortitis or aneurysm which are not common, or a congenital malformation or deformity as a patent ductus arteriosus, that may give rise to a systolic thrill and murmur in the pulmonic area. The great increase in retromanubrial dullness generally suffices to differentiate these conditions particularly when confirmed by fluoroscopic and roentgenographic studies. These can be but usually are not present without diastolic murmurs but the continuous murmur of patent ductus arteriosus is accompanied by a markedly accentuated pulmonic second sound.

The *prognosis* depends upon the degree of obstruction and cyanosis. Intercurrent respiratory infections are common and lead to dissolution more frequently than does heart failure. Associated lesions probably modify the prognosis, but to what extent is difficult to establish. The life span of the patient with pulmonic stenosis usually is short.

Treatment of Chronic Cardiac Valvular Disease

There is unfortunately no direct or specific medical treatment nor any perfected, surgical plastic technique for scarred heart valves. In the early stages of valvular disease absolute rest is advised for a period of a month or two after the acute infection has subsided in order to reduce to a minimum and consequently to decrease the stimulus to proliferation to a low level. It may be considered justifiable to expose those individuals who are known to have a tendency to keloid proliferation during scar formation to x ray treatment as suggested by Golden and Levy. Passive movements of the legs and massage upward even to the abdomen should be used during confinement of the patient to bed. Restrictions in physical activities are desirable for a few months during convalescence but these rulings should be reasonable and proper for the individual. The physician should not keep the patient bedridden or make him a chronic invalid for a year or more. As soon as he can be rehabilitated he should be encouraged to undertake some sedentary occupation. He must be taught to adjust his life to his handicap without making him a cardiac neurotic or unpleasantly heart conscious. Physical effort or exertion should be limited as necessary to earn the livelihood to keep him content. Walking on the level at a moderate or slow pace is beneficial. Such muscular action helps the venous return from the lower extremities.

The patient who has suffered cardiac valvular disease should never be allowed to take any strenuous physical work nor to indulge in competitive athletics Further details as to limitations of activities usually may be left in the hands of the intelligent patient especially one who has been reeducated He must be taught to make sanguine observations and recognize that any effort that produces breathlessness or heart pain should be avoided and thus he can establish his own exercise tolerance The development of symptoms should convince him that he has overstepped his limitations and he must learn to stop short of this Reclining at rest in a horizontal position with head elevated enough to prevent dyspnea at regular intervals during the day certainly after the midday meal for at least an hour will do much to prolong a comfortable existence Rest periods should be adjusted according to the grade of the valvular disease Sleep for ten hours each night should be insured if necessary by the use of sedatives

Life is easier for victims of chronic cardiac valvular disease in an equable climate and at moderate to low altitudes If it is possible chronic cardiopaths particularly those whose lesions were of rheumatic fever origin should be moved away from damp abodes along rivers where cellar floods are common Particularly if the patient lives in the North he most certainly should be advised to get away from the rigors of winter if he can do so Prophylactic salicylate and sulfonamide therapy should be carried out in rheumatic children each winter Warm dry parts of the country with moderate altitude are most promising for prevention of recurrences and most conducive to maintenance of circulatory equilibrium for longer years

The diet should be well balanced and particular care should be taken to see that the protein and vitamin contents are normal Besides these basic requirements a caloric intake of about 2 000 should be prescribed It should be such that the patient does not gain weight even though life is sedentary In the case of obese weak individuals it is especially desirable to restrict total caloric intake This should reduce gradually the obese patient s body weight at the rate of not more than a pound a week until he is back to his accepted body weight

Small meals with five and six servings at short intervals are much to be preferred to any large meals during the day Banquets should be avoided The fluids should be moderately restricted especially at the meals and a total of 3 liters a day should be sufficient unless it is extremely hot Carbohydrates such as jellies candies fresh fruit juices milk sugar soda crackers and toast should make up the bulk of the calories Foods that produce gaseous distention or allergic reaction should be avoided Gastric distention mechanically moves up the left leaf of the diaphragm anteriorly and the heart usually slips off posteriorly and its action is embarrassed It is quite undesirable and it usually is unsafe to allow the patient to drink ice cold liquids It is known that if these are swal

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Carbohydrates that do not produce flatulence are highly desirable foods Inulin, which is present in considerable amounts in artichokes has been reported to have the most beneficial supportive effect for the undernourished myocardium Gelatin likewise is a desirable food but because of its high content 25 per cent, of glycocoll or aminoacetic acid which is of some importance in muscle metabolism It should be given as a paste made of a dry powder moistened with orange juice or any other fluid in 5 gram doses 3 times a day for a week and then once a week Delicate easily digestible proteins of high biological value such as fowl breast fish eggs milk especially buttermilk are desirable Cereal preparations, cooked fruits, vegetable purees asparagus cauliflower, carrots or fresh avocado along with juices of orange and grapefruit and baked stewed or canned fruits that do not ferment easily have an additional mild laxative value Mineral oil fortified with carotene is the most desirable extra laxative if such is needed

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General therapeutic indications are for the most part for symptomatic treatment No drugs of course could directly effect any changes in the sclerosed valve The heart muscle must be sustained by dietary means as long as this is possible It would seem rational to try to help to remove the byproducts of increased work necessitated by the valvular deformities in the myocardium by maintaining at as high a level as possible the circulation in the heart muscle and myocardium by the use of vasodilators such as theophylline and possibly theobromine derivatives It was emphasized by Dr Christian that cardiac fatigue may be relieved by daily tonic doses of 0 1 to 0 2 gm (gr 1½ to 3) of powdered leaf of digitalis There was a suggestion made also that such administration of digitalis has a desirable limiting effect on the degree of heart hypertrophy

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Patients with chronic cardiac valvular disease are prone to the secondary engraftment of subacute bacterial endocarditis upon the scarred endocardium Prophylactic treatment with sulfonamides particularly with sulfadiazine is indicated at the time of acute respiratory infections or just before the extraction of teeth or before the removal of tonsils or before any other septic surgical procedures such as the draining of an antrum or an infected gallbladder The sulfonamide will prevent by its bacteriostatic effect the multiplication of organisms that get into the blood stream under such circumstances and this will tend to prevent lodging of these on areas of valvular damage For patients who are having recurrent bouts of rheumatic fever antirheumatic salicylate or sulfonamide therapy should be continued for months in adequate dosage to prevent recrudescences Coburn and others [7] have been able to prevent a large number of exacerbations in rheumatic fever patients with continuation of 1 to 2 gm (gr 15 to 30) doses of sulfonamides daily from October to June

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There are certain undesirable food stuffs, particularly the gas forming foods such as dried beans and at times cabbage, brussel sprouts onions turnips, radishes, green peppers and cucumbers Concentrated proteins such as cheese often are not well tolerated Moderate restrictions of total caloric intake and of salt and water intake should be encouraged

General therapeutic indications are for the most part for symptomatic treatment No drugs of course could directly effect any changes in the sclerosed valve The heart muscle must be sustained by dietary means as long as this is possible It would seem rational to try to help to remove the byproducts of increased work necessitated by the valvular deformities in the myocardium by maintaining at as high a level as possible the circulation in the heart muscle and myocardium by the use of vasodilators such as theophylline and possibly theobromine derivatives It was emphasized by Dr Christian that cardiac fatigue may be relieved by daily tonic doses of 0 1 to 0 2 gm (gr 1½ to 3) of powdered leaf of digitalis There was a suggestion made also that such administration of digitalis has a desirable limiting effect on the degree of heart hypertrophy

Certain patients particularly those with mitral stenosis according to some must be kept below toxic level of digitalization so as to prevent the precipitation of atrial fibrillation This serious disorder of cardiac mechanism sooner or later develops It usually persists after it has once developed Of course in patients with mitral stenosis with fibrillation by further digitalization good function may be maintained by keeping the ventricular rate at a low level of 60 to 70 per minute In general normal sinus atrial mechanism is more conservative and should be maintained as long as it is possible to do so Some advise the use of quinidine

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CHAPTER XIII B

NON VALVULAR HEART DISEASE

By Henry A Christian

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Definition—The term non valvular heart disease is used in this chapter for that form of heart disease in which myocardial insufficiency with or without myocarditis has developed in the absence of lesions of heart valves or pericardium

The discussion of non valvular heart disease will be presented under the following subtitles

PART I

MYOCARDITIS

Acute and Subacute Myocarditis

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PART II

CHRONIC NON VALVULAR HEART DISEASE

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This is an arrangement for convenience of discussion Obviously it is not a definite or logical pathological or clinical classification but it would seem to be a practical useful method of bringing together under one general heading the discussion of a group of patients with heart disease patients who show many similar features and who stand out in contrast to patients with acute and chronic lesions of valves or pericardium discussed in other chapters in Oxford Medicine

PART I

MYOCARDITIS

Definition—The term myocarditis is used to indicate the presence in the myocardium of a pathological lesion consisting of focal or diffuse degeneration of muscle cells cell infiltration of the interstitial tissue of the heart and often with the cell infiltration proliferation of the connective tissue framework of the myocardium ranging from young granulation tissue to mature fibrous or scar tissue

The term *myocarditis*, is a pathological one but it is used also in a clinical sense as the name for the forms of cardiac insufficiency resulting from the pathological lesion myocarditis

The term *myocardial insufficiency* is a clinical one used where there is evidence during life of failure of the heart muscle to function with normal efficiency. When myocardial insufficiency is marked the term *congestive failure* is much used. With myocardial insufficiency the heart muscle may or may not show myocarditis as defined in the previous paragraph.

These myocardial conditions may be subdivided into acute, subacute and chronic. Since the demarcation between acute and subacute is not very definite either pathologically or clinically, it seems satisfactory in the subsequent discussion to group acute and subacute together. Consequently I will describe myocarditis under the subheadings 1) *acute and subacute* and 2) *chronic*.

Acute and Subacute Myocarditis

Incidence

Slight, Non Progressive Myocarditis.—Slight, non progressive acute and subacute myocarditis, if we make the diagnosis from changes in the electrocardiogram, most often lengthening of the P-R interval and change in the T waves, is frequent in occurrence, particularly during the course of an acute infectious disease[11, 2]. Such electrocardiographic changes are almost the rule in acute rheumatic fever, and their presence is accepted generally by physicians as evidence that a lesion, myocarditis, has developed in the myocardium during the course of rheumatic fever even though these changes disappear from the electrocardiograms of the great majority of these patients during convalescence from their rheumatic fever. The appearance of changes in electrocardiograms during rheumatic fever is accepted by almost every one as evidence that the rheumatic fever has involved the heart, and so long as they persist this is taken as one of the evidences of continuance of activity of the disease, rheumatic fever.

In view of what has just been stated for rheumatic fever, it seems strange that the medical profession has been very slow to accept changes in the electrocardiogram, similar to those that occur in rheumatic fever, as diagnostic of myocarditis during the course of acute infectious disease other than rheumatic fever, but such seems to be the case.

Recent electrocardiographic studies during the course of various infectious diseases[11] do indicate a very considerable frequency of such electrocardiograph changes, and these changes now are being considered

as evidence that the myocardium has been involved in a pathological change caused by the causative organism of the given infectious disease

As in rheumatic fever the changes in the electrocardiogram usually disappear as the patient recovers So far there have not been sufficient electrocardiographic study in the various infectious diseases to indicate the actual frequency of the occurrence in them of such lesions in the myocardium Moreover, it is to be remembered that in a patient with rheumatic fever the changes in the electrocardiogram may be present for only a short time Consequently unless electrocardiograms are made with great frequency, certainly daily until characteristic changes are seen, it can not be stated that the patient under study has shown no electrocardiographic evidence of myocardial involvement The same obviously would apply in the study of any infectious disease in relation to the occurrence of a myocardial lesion However it is probable that in these other infectious diseases they do not occur with any such frequency as in rheumatic fever

Progressing or Fatal Myocarditis—Progressing acute and subacute myocarditis is relatively infrequent in occurrence whether we accept the presence of continuing changes in the electrocardiograms persisting clinical symptoms and signs or gross or microscopic abnormality in the heart muscle as evidence Fatal acute or subacute myocarditis is somewhat less frequent No studies are available to express statistically the rate of incidence of this progressing type of myocarditis but recently published reports indicate that the frequency of their occurence is greater than had been believed during the earlier periods of time There are reports which show that lesions of acute and subacute myocarditis are present in the hearts of numerous of the patients who have died during the course of almost every one of the recognized infectious diseases but as a rule these myocardial lesions are not very extensive play no significant role in causing death and probably would be recovered from had the patient survived his infectious disease or infection [3 42 93] These patients properly even though they died should be grouped as slight non progressing myocarditis A much smaller number of patients who die during an infectious disease or infection show the more extensive myocardial lesions[94] which undoubtedly play some part in the fatal progression of the case and an occasional patient has such extensive lesions in the myocardium that death seems directly related to them Circulatory failure with death in infectious diseases and infections more frequently results from what is called the circulatory failure of acute infectious disease than from myocarditis

Both of these types of myocarditis may be encountered also when there is a focus of infection elsewhere in the body than in the heart muscle In the aggregate these latter cases are not very numerous and with newer chemotherapy of localized infections they should be becoming decidedly infrequent

Isolated Myocarditis—Of very great interest are the reports of patients with evidences of the presence of acute or subacute myocarditis, in whom no recognized, prior, infectious disease or infection was present, and in whom except for the lesions in the myocardium, very little that was abnormal was revealed on postmortem examination Among the names used for this type of myocarditis the term, isolated myocarditis expresses well the situation i e it is an inflammatory process isolated in, or confined to the myocardium Other terms for it will be given later on in this chapter, when this form of myocarditis again is discussed This form of myocarditis is infrequent, for since first described in 1899 by Fiedler only about 70 cases of it have been found in the literature by me[28, 85]

Etiology of Acute and Subacute Myocarditis

Slight, Non progressing Myocarditis—In the great majority of cases with slight non progressing acute or subacute myocarditis, cases referred to in the first paragraph of the preceding section on Incidence[1, 10, 2, 81] the etiology is that of the infectious disease or the local infection accompanying or preceding the electrocardiographic evidence of lesion in the myocardium Just how the lesion in the myocardium is produced remains at present under debate Is it the direct effect of the presence in the heart muscle of the etiological factor? Is it the direct results of injurious action of some circulating toxic product of the etiological factor generated somewhere in the body outside the heart? Is it of the nature of an allergenic response of a sensitized tissue to a circulating allergen? In different infectious diseases and local infections sometimes the one, sometimes another of these explanations seems best to explain what is happening or has happened in the myocardium

Progressive or Fatal Myocarditis—In the patients with progressive or fatal acute or subacute myocarditis an accompanying or preceding infectious disease or infection usually is the cause

Isolated Myocarditis—A very important group[28, 5] although not a large one is isolated myocarditis already referred to The etiology of these cases remains essentially unproved For them there is the possibility

of a specific virus as etiological factor supported by the demonstration in animals with myocardial lesions histologically like those found in man of the presence of a causative virus that can be passed from animal to animal with the repetition of acute or subacute myocarditic lesions[4,10] However so far no such virus has been isolated from human cases of acute or subacute myocarditis by animal inoculation or other method applicable to the study of viruses but Smadel and Warren have demonstrated in patients with three day fever in Manila a disease characterized by chills fever severe headache and usually pleocytosis of spinal fluid, an appreciable amount of specific neutralizing antibody for the virus of encephalomyocarditis a virus which had been isolated from a chimpanzee in Florida and which caused lesions in both brain and myocardium of rodents and monkeys infected with it

That a toxin or other chemical might be causative of diffuse or focal acute or subacute progressive myocarditis in man has some further support in the fact that in rabbits such myocarditic lesions can be produced by properly spaced and properly dosed injections of adrenalin chloride and sparteine sulfate a type of change which about 38 years ago received considerable study in my own laboratory by I Chandler Walker Other chemicals have been reported as causing lesions of a myocarditic nature Among these of especial clinical interest are the sulfonamides[41,51,53] and the arsenicals[36,8] since here the question arises in each patient is the chemical the cause of the lesions in the myocardium or is the infectious disease under treatment the cause However there is evidence from animal experiments[41] that a sulfonamide can be the cause of myocardial lesions similar to those seen in patients who have received a sulfonamide These studies show that simple chemical substances can damage heart muscle with an histological response not unlike that seen in the myocardium of some patients dying as the result of acute or subacute myocarditis

In man some fatal cases of diphtheria show myocarditic lesions[53] very probably caused by diphtheria toxin In tetanus also there may be myocarditic lesions caused by the tetanus toxin In most infectious diseases and infections however there is very little evidence for the action on the heart muscle of a soluble toxin

Syphilis rarely is the cause of myocarditis in postmortem examination of patients In view of the frequency of syphilitic aortitis and of syphilitic lesions of the aortic valves this infrequency of syphilitic myocardial lesions is surprising Warthin[49] at one time described a form of syphilitic myocarditis basing the syphilitic etiology on finding spiro

chetes (treponemes) in the myocardium However, many believe that the so-called spirochetes were the result of the technic, i e, were arte facts The clinical history of these patients and the histological changes strongly suggest that these were cases of isolated myocarditis of non-syphilitic etiology If this is allowed then syphilis remains as a rare cause of myocarditis A few cases have shown scattered small gummata Large gummas do occur in the heart muscle but infrequently, they hardly would be confused with acute or subacute myocarditis

Pathology and Pathological Physiology of Acute and Subacute Myocarditis

Slight, Non-progressive Myocarditis —The lesions in the heart of what in the previous sections has been called slight non-progressive acute and subacute myocarditis the presence of which is demonstrated by changes usually temporary in electrocardiograms, is largely a matter of speculation since opportunity to study such hearts by technics of pathology is infrequent When death occurs in such patients as have shown these electrocardiographic changes the myocardial lesions, which are found [3 21 5], may be more extensive and more advanced than were present in those patients who recovered and with recovery ceased to show the changes that had been seen in their electrocardiograms However from what has been seen in the fatal cases it may be assumed with some probable certainty that the electrocardiographic changes have resulted from three possible lesions of the myocardium, all probably focal in distribution These are edema and cell infiltration including red blood cells (hemorrhages), of interstitial tissue and muscle fibers and/or degenerative changes of the muscle fibers, all of which up to a certain degree of intensity can be thought of as reversible with restoration to normal of the functional integrity of the myocardium There seems little doubt but that any of these changes would be capable of causing prolongation of P-R time or partial or complete A-V block and changes in the ventricular complex in different leads especially changes in the T wave and that up to a certain point of severity or intensity any or all of these changes could disappear with restoration of normal structure and/or function Presumably that is what does happen in these patients

Myocardial Lesions Demonstrated in Patients Dead of an Infectious Disease —When patients die during or following the acute course of an infectious disease or infection outside the heart in the myocardium are

found with varying frequency focal lesions of edema cell infiltration and degeneration of the muscle cells ranging from edema, granular or fatty degeneration and changes in or loss of striations up to hyaline transformation and even necrosis along with swelling shrinkage or eventual disappearance of muscle nuclei[3, 4, 5, 91] The infiltrating cells may be red blood cells polynuclear leucocytes lymphocytes plasma cells or large mononuclear cells their proportion varying in different patients sometimes with a cell composition which is almost pathognomonic of the causative infectious disease as with the so-called Aschoff body or nodule of rheumatic fever in which endothelial cells some multinucleated, predominate Myocardial lesions of these appearances have been described in patients dying during the course of many of the infectious diseases or from an inflammatory lesion elsewhere than in the heart In these hearts mural thrombi sometimes form

The lesions just described except mural thrombi are focal usually small and probably are an unimportant factor in the clinical course or eventual fatality of the causative infectious disease

Progressive or Fatal Myocarditis—The lesions just described although remaining focal may in some patients be very numerous so as to involve a relatively large proportion of the myocardium or even be diffuse in distribution When such extensive distributions occur cardiac function will be disturbed with the appearance of symptoms and signs referable to the cardiac lesion with the probability of progression early or late to a fatal outcome In these patients there will be found a very extensive cell infiltration sometimes polynuclear sometimes mononuclear of the myocardium

In some of the patients particularly those with progressive or fatal myocarditis discussed in the previous sections the time interval between the commencement of lesion in the myocardium and the death of the patient is sufficient to allow of the development of proliferative changes in the interstitial connective tissues with increase in connective tissue cells formation of new connective tissue fibrils and invasion of it by newly formed blood vessels[91] In other words a granulation tissue forms as is usual in the evolution of the lesions of inflammation Such newly formed connective tissue will replace degenerating and disappearing muscle fibers if their injury has been extensive The muscle fibers in these hearts will show degenerative changes often extensively distributed at other times in focal groups of varying size This is particularly true when proliferative changes are seen in the interstitial tissue The degenerative changes in muscle cells range from granular fatty

or hydropic degeneration to hyaline transformation, fragmentation, atrophy, necrosis with disappearance completely of many muscle fibers

Often the lesions already described have a perivascular situation so that small blood vessels in the myocardium show cellular infiltration of their adventitia and of their supporting connective tissue framework At times also degeneration particularly hyaline degeneration and/or cell infiltration appears in the media and intima of the blood vessels and their lumens may be decreased in size Even thrombi may form to block small vessels

In the gross the hearts whose pathology so far has been described may seem normal or moderately dilated This is the usual finding but some may show slight to moderate increase in weight i e show hypertrophy They tend to be flabby often a little paler than normal on section grayish red rather than the usual red of normal heart muscle Rarely a heart on section has a grayish boiled appearance or a yellowish hue These color changes may be in scattered, small rounded areas or linear streaks or be diffuse Some hearts show a punctate appearance especially a yellowish punctate or tigroid appearance Sometimes punctate hemorrhages are seen Valves are normal Occasionally there are small subendocardial and/or subpericardial hemorrhages Very often hearts whose myocardium under the microscope shows definite even considerable abnormality in the gross appear normal Certainly microscopic examination of sections from many parts of the heart are needed if one is not going to miss the presence or greatly underrate the extent of myocarditic lesions

Isolated Acute and Subacute Myocarditis[illegible] —The term isolated myocarditis is used for patients in whom an inflammatory lesion appears in the myocardium without there being evidence of any general infectious process or any inflammatory lesion in the body except the one in the myocardium Other terms used for this lesion are primary acute or subacute myocarditis primary acute interstitial myocarditis Fiedler's myocarditis myocarditis perniciosa acute non specific myocarditis

In hearts of this type pathological lesions are very much more marked than in most of the hearts of the categories described in the preceding sections The hearts of isolated myocarditis as a rule show dilatation and hypertrophy, often of considerable amount The heart muscle on section seems more moist than normal and focally or diffusely shows change in color grayish more than red in hue except that in some hearts areas of hemorrhage brighter red in color or yellowish areas of fatty change are observed A considerable frequency of mural thrombosis

occurs in these patients and emboli from these often go into and block areas of either the pulmonary or systemic peripheral circulation, these may cause important features in the symptomatology of isolated myocarditis

The microscopic lesions of isolated myocarditis are not at all specific although their extent gives to the myocardium a rather characteristic appearance Cases may be subdivided into those with diffuse and those with focal lesions For the latter the term, granulomatous is used by some In those dying after a shorter period of illness edema, cell infiltration and muscle cell degeneration are the chief changes In very acute cases polynuclear leucocytes make up the bulk of the infiltrating cells they being present both in the interstitial tissue and within degenerated muscle cells In somewhat less acute cases polynuclears decrease, and mononuclears increase the latter being lymphocytes plasma cells and endothelial mononuclears in varying proportions along with a decreasing proportion of polynuclears In some cases the endothelial mononuclears are particularly prominent even sometimes in character and arrangement suggestive of diffuse Aschoff bodies although usually the giant cells of the rheumatic Aschoff body are lacking Infrequently a considerable number of eosinophiles are seen and rarely mast cells In these cases scattered or even many muscle cells almost always show loss of distinctness of striation a granular or finely fatty myoplasm and large increasingly vesicular nuclei Some of the muscle fibers become hyaline stain less well and show smaller pyknotic nuclei Some muscle fibers even in the acute cases lose their staining reaction i e become necrotic and begin to fragment atrophy and disappear In some hearts red blood cells appear among the cells in the interstitial tissue or even within degenerated muscle cells and may aggregate to form distince focal hemorrhages

If the process is of somewhat longer duration connective tissue cells multiply and young connective tissue fibrils are laid down This occurs between muscle cells and gradually will replace degenerated ones to form foci of cellular, young connective tissue into which later blood vessels bud as in granulation tissue These cases correctly should be termed subacute rather than acute

The pathological physiology of these hearts with acute and subacute myocarditis can be summed up as follows *Dilatation takes place because* of injury to the heart muscle which decreases strength of contraction in systole and increases relaxation in diastole Cardiac cavities enlarge i e dilate so that they contain more blood for systolic output With lessened efficiency of contraction systolic output decreases and becomes

incomplete so that more and more blood is left in the heart at the end of each systole This adds further increments to dilatation of the cardiac cavities This cycle can progress rapidly to an increasing cardiac insufficiency and death in a short time from acute cardiac decompensation[49] With less rapid progression the thinned myocardium responds by hypertrophy, and a cycle of increase in size of cardiac cavity leading to increase in thickness of the muscle wall sets in to result in a progressing dilatation and hypertrophy causing a progressing increment in heart size and heart weight with or without cardiac insufficiency, depending on the ability of the injured heart muscle to maintain a systolic output compatible with the circulatory needs of the body When the latter fails, cardiac decompensation sets in which if it continues ends in death to the patient In the earlier stages if muscle injury ends, restitution to normal integrity of the heart is possible and the patient recovers If this does not take place, evidences of cardiac insufficiency continue and progress rapidly or slowly through the stages of acute and subacute to chronic

The pathological processes in the heart which have been described so far, act injuriously in four ways (1) Injured muscle fibers contract and relax with lessened efficiency (2) Edema, interstitial cell infiltration and increase in connective tissue elements hinder nutrition of muscle fibers whether they are normal or degenerated and this interferes with normal systole and diastole (3) Focal lesions initiate arrhythmias to decrease efficiency of function of the heart muscle (4) In contraction and relaxation of heart muscle a cycle of chemical changes goes on in which oxydative processes play an important part The lesions already described can and do retard oxydation by causing a partial intracellular anoxemia It seems highly probable that this anoxemia can occur in muscle cells which still appear normal in appearance This would explain the occasional fatal case in which thorough study of the myocardium shows very slight or even no change in its appearance beyond possibly some hypertrophy of muscle fibers

In patients with severe infections or infectious diseases in whom marked circulatory inefficiency appears another mechanism is concerned in the pathological physiology other than the effects of the lesions in the myocardium This is termed by many the *circulatory failure of acute infectious disease* It may develop in the absence of any satisfactory evidence of myocardial lesion although usually there is present also some degree of myocarditis This circulatory failure of acute infectious disease is a form of shock and analogous to so called surgical shock

post traumatic shock and the shock of severe burns hemorrhage and adrenal insufficiency Such shock has been investigated very thoroughly both in the laboratories of experimental medicine and surgery and in the clinics with the application of many technical methods Numerous theories as to its mechanism have been advanced many of which subsequently have been disproved A reasonably satisfactory explanation of its pathological physiology recently has been summarized as follows by Stead[80]

Patients with acute infectious diseases frequently develop the clinical picture of shock before they die Because the usual picture of congestive failure is absent and because the circulation does not improve with the administration of digitalis frequently it is stated that the patient has peripheral circulatory failure or shock, and that the circulation fails because of an inadequate venous return to the heart Observations were made on a group of patients with the clinical picture of shock produced by acute infections By staying constantly present with all patients admitted with an overwhelming infection it was possible to obtain data before and during the period of circulatory failure When the course was unfavorable the circulation failed The patient became cold and pale and the pulse pressure narrowed At this time the physician in charge usually made the diagnosis of peripheral circulatory failure or shock Studies of the blood in such patients showed that the plasma volume was normal and that there was no evidence of hemoconcentration The vasomotor centers functioned normally because blocking the nerves to a cold extremity caused the extremity to become warmer These studies eliminated a decrease in blood volume or a failure in the vasomotor centers as the cause of the circulatory failure The possibility still existed that the shock might be caused by failure of the venous return from pooling of blood in dilated splanchnic veins If pooling of blood in dilated veins and a decrease in effective venous pressure in the right auricle were responsible for the circulatory failure raising the venous pressure would improve the circulation The venous pressure was therefore recorded by inserting a needle in the external jugular or femoral veins Plasma blood and glucose solution then were given rapidly until the veins of the body were engorged and until the venous pressure was elevated The circulation did not improve demonstrating that the circulatory failure was not caused by an inadequate venous return The data suggested that the heart was at least in part at fault and that the circulation could not be restored to normal by raising the venous pressure Other studies have shown that none of the circulatory system

functioned normally The infection had produced widespread metabolic disturbances in cell metabolism throughout the body, and the cells were slowly dying The circulatory failure was secondary to a general failure in metabolism Treatment with transfusions and digitalis was useless If the infection could be controlled the circulation improved If it could not be the patient died

This has the merit of recognizing the complexity of the pathological physiology and of placing the blame on the generally deleterious cellular effects of the infection rather than on any particular part of the circulatory mechanism

Symptoms and Signs of Acute and Subacute Myocarditis

In many of the patients who during the course of an infectious disease or of an infection develop electrocardiographic evidence of a lesion in the myocardium a myocarditis there are no symptoms and no signs to indicate this The symptoms are only such as would be expected from the infectious disease or infection Except for the changes in the electrocardiograms changes to be described in some detail in the section on Diagnosis there is nothing to indicate a cardiac lesion

In other patients however, there are slight symptoms and signs pointing to a probable myocarditis There is a little breathlessness, slight tachypnea and dyspnea slight precordial discomfort tachycardia out of proportion to the patient's fever rarely bradycardia sometimes consciousness of an arrhythmia some pallor or slight cyanosis, possibly an increased area of apex impulse, a gallop rhythm, a soft apical systolic murmur and rarely scattered, fine rales at the bases of the lungs posteriorly Very often blood pressure is lower than normal, its decrease may be followed in some patients as the myocardial lesion progresses Some or all of these may develop in the individual case The presence of a soft systolic murmur cannot be considered to be of any real significance in diagnosis unless it has been observed to appear during the course of the illness and is accompanied by electrocardiographic abnormalities

In a few patients all of these symptoms and signs are prominent and definite enlargement of the heart is present demonstrated either by physical examination or by x-ray study[28] In some of these the symptoms and signs increase and the patient develops various evidences of cardiac decompensation including right upper quadrant abdominal tenderness with enlargement of the liver and slight to moderate jaundice dyspnea cough and basal rales in the lungs slight to moderate edema of

dependent parts and cyanosis or pallor Precordial distress occurs with considerable frequency In an occasional patient embolism of the pulmonary vessels with infarction of the lung or of a peripheral artery with sudden blocking of the blood flow in it may occur to cause characteristic symptoms and signs This may happen in a patient previously showing nothing to suggest the presence of myocarditis even in a patient up to the time of this happening seemingly well the sudden pain of the embolism being the first intimation that not all was well with the circulation[49]

Fever and leucocytosis are common but of course both may be caused by the infectious disease or infection of the patient that has preceded or accompanies the myocarditis However an increase in fever and leucocytosis may be and often is indicative of the development of myocarditis In cases of isolated myocarditis fever and leucocytosis are very significant evidences of this acute inflammatory process

The various symptoms and signs already enumerated are the expected evidences of isolated myocarditis a condition which should be seriously considered when they appear, especially with fever and leucocytosis in a patient in whom there are no evidences of a general or localized infection or an infectious disease Here as in all other patients suspected of having acute myocarditis the appearance of electrocardiographic changes is a most important item in diagnosis

In a few patients particularly those with isolated myocarditis precordial pain localized or radiating to arm and/or neck is so striking a symptom as to suggest cardiac infarction, a diagnosis which may find some support from the abnormalities seen in electrocardiograms In these patients as well as in others without precordial pain there may be sudden death or death shortly after a stage of circulatory collapse Autopsy of them usually will fail to show just why sudden death came cardiac infarction is not found Possibly in these ventricular fibrillation has developed

In very many patients with acute or subacute myocarditis particularly those with very slight symptoms and signs of cardiac involvement symptoms and signs disappear and electrocardiograms return to their normal appearance Recovery has been complete In some the changes continue or increase and complete recovery does not take place For some of these eventual progression into continued cardiac decompensation with its usual symptoms and signs may be expected This may be relatively a rapid or a very slow progression Accordingly these patients may be given the diagnosis of subacute or chronic myocarditis

Rheumatic fever differs from the other infectious diseases in that slight evidence of myocardial lesion during the acute attack indicates a great probability of subsequent development of progressing rheumatic heart disease even though apparent complete recovery has taken place the progression in the great majority of the patients depending on valvular rather than myocardial lesions Hence the occurrence of changes suggesting myocardial involvement during rheumatic fever is a far more serious phenomenon than their occurrence in other of the infectious diseases and infections in which the probability of a progressively continuing, cardiac insufficiency is after all not great for in these patients unlike those with rheumatic fever valve lesions do not appear

Diagnosis of Acute and Subacute Myocarditis

Change in the electrocardiogram is the most important diagnostic sign of this form of heart disease often it is the only one The two most frequent electrocardiographic changes are 1) prolongation of A-V conduction time i e lengthening of the P R interval and) depression of the T wave [3 4 8 10 1 15 18 19 1 2] With lengthening of the P-R interval in some patients partial or even complete A V block may develop T waves may flatten out become biphasic or become inverted, even V-shaped The T wave change may appear in any or all leads, frequently it appears only in lead II of the conventional I II and III leads In some patients QRS complex changes with slurring notching, splitting or flattening or even the changes of intraventricular block develop The appearance of extrasystoles is not infrequent Rarely auricular tachycardia or fibrillation develops Possibly in sudden death there may have been ventricular fibrillation In very many patients these abnormalities in the electrocardiograms particularly the lesser ones disappear during convalescence but they may persist for several weeks or months eventually to go In some, even without other evidence of cardiac lesion they do persist certainly for a long time

The various symptoms and signs discussed in the preceding section always should suggest the development of acute or subacute myocarditis and when combined with the appearance of prolonged P-R interval and T wave changes make that diagnosis almost a certainty

If with the presence of these changes in the electrocardiogram there are symptoms and signs of cardiac disease as described in the previous

section along with fever and leucocytosis in a patient who has no evidence of infection outside the heart or of infectious disease a diagnosis of acute or subacute isolated myocarditis should be made

In infections and infectious diseases a diagnostic distinction between myocarditis and the circulatory failure of acute infectious disease should be made as far as that is possible because the treatment should depend on which factor is acting or at least on which is dominating the clinical picture shown by the patient In the circulatory failure of acute infectious disease as a rule, the patient s general condition is worse than when the condition is only myocarditis This is shown particularly by the rapid pulse of poor quality often called thready the falling blood pressure the usual grayish pallor with cool sweating and cool extremities the weak heart sounds the nausea and vomiting the collapsed condition of the patient both general and cerebral and the poor response to all kinds of treatment With this clinical picture the diagnosis of circulatory failure of acute infectious disease should be made instead of or in addition to that of acute myocarditis depending on whether there is present also signs and symptoms of cardiac disease

Prognosis of Acute and Subacute Myocarditis

From the statements preceding this section it is very obvious that the patient with evidences of acute or subacute myocarditis may be either mildly or severely ill more being in the former than in the latter group The great majority recover from the illness many with no residual signs of heart disease Some of the severely ill recover but are left with evidences of a diseased heart these finally should be called cases of chronic myocarditis Some of them do not survive This is particularly true of those on whom the diagnosis of isolated myocarditis is made In them mortality has been very high possibly because that diagnosis has been made in only the very severely sick patients In some patients the course of the illness is rapid and death comes within 7 to 10 days In others the course is longer but still the disease is fatal Some of the patients die suddenly and unexpectedly as described in the section on Symptoms and Signs In all of this group of patients the appearance of symptoms and signs of the circulatory failure of acute infectious disease makes the prognosis much worse If the evidences of this continue soon it becomes an irreversible process with certain death In all of these patients recent improvements in the treatment of infections and

infectious diseases in particular treatment by chemotherapy, should improve greatly the prognosis

Treatment of Acute and Subacute Myocarditis

The prompt and thorough treatment of antecedent or accompanying acute infections and infectious diseases is the most effective for most patients with acute and subacute myocarditis This should greatly decrease the incidence of myocarditis If in this group of patients there develop any symptoms or signs of cardiac involvement, continued bed rest becomes imperative as in the regime generally advised for cardiac involvement during or following an attack of rheumatic fever Dehydration should be avoided but care should be taken not to overload the circulation by a fluid-intake beyond what is needed to offset dehydration Excessive fluid intake by mouth or by giving intravenously fluids including blood and blood derivatives, is to be avoided Diet should be of adequate calorie content, not bulky, as normally balanced as possible as to protein carbohydrate and fat, containing an optimum amount of vitamins diet as at present regarded as appropriate for patients with acute infections or infectious disease The sweating patient needs added sodium chloride in the fluid being given to prevent his dehydration, if lost sodium chloride is not replaced, the deficiency in itself is deleterious

Digitalis is indicated only if there develops pulmonary or peripheral edema including hepatic tenderness and enlargement Intravenous use of some of the suitable digitalis preparations is preferable for these patients Unfortunately digitalis is apt to be disappointing in its effects If an arrhythmia such as auricular tachycardia or fibrillation appears it should be treated by methods usually advised Of the various circulatory stimulants caffeine and coramine seem preferable but are not very effective With falling blood pressure epinephrin may be given with at times some seeming advantage For the cyanotic patient oxygen inhalation is desirable

If symptoms and signs indicate serious myocardial involvement unfortunately no treatment is really satisfactory The most important item in therapy should be to treat the infection or infectious disease from its beginning so well that myocardial lesions either do not develop or do not become extensive, such prophylaxis is as a rule effective

CHRONIC MYOCARDITIS

Incidence

Chronic myocarditis in the sense of the presence of this pathological lesion of an extent to be an important causative factor in cardiac decompensation is of infrequent incidence This infrequency is in striking contrast to the very considerable frequency of the several forms or types of acute and subacute myocarditis already discussed which is another way of saying that the great majority of patients who have signs and symptoms of acute and subacute myocarditis rheumatic myocarditis being excepted do not in their subsequent years have any excess probability of developing chronic cardiac disease of any type The rheumatic cases have a high probability of developing chronic cardiac valvular disease

Etiology of Chronic Myocarditis

If chronic myocarditis has been preceded by acute or subacute myocarditis the etiology is that described already for them In the absence of this etiology is unknown this being analogous to the situation for acute and subacute isolated myocarditis For this group of unknown etiology the term chronic isolated myocarditis is appropriate and may be used

Pathology and Pathological Physiology of Chronic Myocarditis

The lesions of chronic myocarditis [9,61,65,67,68,69,70] may be focal or diffuse more often the former Small foci of chronic myocarditis which are found frequently in the hearts of patients dying of heart disease probably play no role in cardiac decompensation particularly in its fatal form With extensive focal or diffuse chronic myocarditis the hearts in the gross have the same general appearance Their cavities are dilated their walls hypertrophied the relative degree of each varying from heart to heart Valves and pericardium are essentially normal in appearance Many of the hearts on section show a mottled or diffuse grayish red color of the myocardium while some are dark red Often the muscle

feels unusually firm and it may cut with a very slightly gritty resistance Some of these hearts are very large and heavy, practically all weigh more than is normal in proportion to body height and weight Both hypertrophy and dilatation are present but in varying degree in individual patients The coronaries may show no slight or marked arteriosclerosis, in a few occlusion with areas of infarction may be found as an incident or complication of chronic myocarditis On microscopic examination there is a focal or diffuse increase in connective tissue, which may be cell rich or cell poor, the cells being almost all monocytes, mainly connective tissue cells plasma cells and lymphocytes in varying proportion The connective tissue may be of loose or dense structure Muscle fibers adjacent to or surrounded by connective tissue proliferation may show degeneration or atrophy Numerous of these fibers disappear in part or in toto and some become hyaline or even necrose Muscle fibers in these hearts away from areas of connective tissue increase usually hypertrophy while those adjacent to or in such areas of connective tissue may show either hypertrophy or atrophy

Chronic myocarditis has several possible paths of development 1) A patient with acute or subacute myocarditis instead of recovering or dying may continue to have evidences of myocardial disease and rapidly or slowly progress into a condition of cardiac decompensation, a condition which in turn may intermit or continue with final death in cardiac decompensation 2) A patient with acute or subacute myocarditis after apparent recovery may again develop evidences of myocardial disease the interval of apparent recovery being short or long, in these patients then progression may be as in patients of the preceeding group 3) A patient without ever showing any evidence of acute or subacute myocarditis may gradually develop evidences of myocardial disease, and these continue into cardiac decompensation It is very difficult to distinguish such patients from those having chronic non valvular heart disease without myocarditis 4) A patient seemingly well and without anything to suggest a prior myocarditis may die suddenly or develop cardiac decompensation and in a short time die In some patients of this last group an embolic phenomenon is the first thing to suggest myocardial disease All of these patients have in common the absence of anything to suggest the presence of diseased valves or pericardium From them are excluded patients who during or following acute rheumatic fever show evidences of myocarditis for these progress very often into chronic valvular heart disease less frequently into chronic pericarditis and are discussed in other chapters of Oxford Medicine

Hearts with chronic myocarditis dilate hypertrophy and fail just as do the hearts discussed in the next chapter on Chronic Non-valvular Heart Disease. The chronic myocarditic lesions contribute however to cardiac failure in these patients, usually accelerating the failure and sometimes being the main cause.

Symptoms and Signs of Chronic Myocarditis[69, 70]

In some patients symptoms and signs as described for acute and subacute myocarditis continue and in time progressively *increase to the* production of symptoms and signs of chronic decompensation as described in a subsequent section headed Chronic Non-valvular Heart Disease. Particularly interesting are those patients in whom this later progression is rapid and the total duration of cardiac decompensation is short[69]. In some of these mural thrombi form before or during the development of cardiac decompensation to make their presence suspected later by the development of the symptoms and signs of embolism[9] when emboli are set free to obstruct arteries in the brain, the extremities, the spleen, the kidneys or the lungs or with great rarity a branch of the coronary arterial system. In some patients with chronic myocarditis precordial distress is prominent and may be such as to suggest myocardial infarction[68]. Occasionally at autopsy myocardial infarction is demonstrated without or with obstruction of a branch of the coronary artery.

Patients with chronic myocarditis show cardiac enlargement often of marked degree, demonstrable on physical examination or with x-ray[8, 9]. In many of these patients a systolic murmur, soft or loud, usually of maximal intensity in the apex region of the precordium develops while in a few also a diastolic murmur suggesting mitral stenosis or aortic insufficiency appears. In these patients incorrect diagnoses of organic valve lesions may be made.

Arrhythmias[6, 8] develop in many of the patients, particularly often auricular fibrillation. Often the electrocardiogram shows disturbances in the conduction system, especially changes in the ventricular complexes.

Diagnosis of Chronic Myocarditis

In some patients the diagnosis will be made correctly from following progression from a recognized acute or subacute myocarditis. In others

it will be made from the great rapidity of progression in a patient known to have an enlarged heart without signs of valvular or pericardial lesion and without preceding high blood pressure Marked abnormality in the ventricular complexes seen in the electrocardiograms indicate probability but are not definitely diagnostic of the lesions of chronic myocarditis Embolic phenomena particularly if repeated suggest the presence of mural thrombi in the heart and these are consistent with a chronic myocarditis in the absence of symptoms pointing toward coronary artery obstruction and infarction of the myocardium All of these symptoms and signs however may develop in patients who at autopsy do not show the lesions of chronic myocarditis Also it is true that in some patients the lesions of chronic myocarditis will be found at autopsy with nothing during life to suggest making that diagnosis of the cause of their cardiac decompensation Chronic myocarditis still remains a condition infrequently diagnosed correctly with errors of both omission and commission

Prognosis of Chronic Myocarditis

Prognosis is poor Chronic myocarditis is a condition which if it becomes extensive will progress to a fatal outcome often after a relative brief period of positive symptoms and signs Duration of life will be moderately increased in many of these patients by the application of suitable therapy as described in the next secetion headed Chronic Non valvular Heart Disease while unfortunately in some it will have little influence on length of life

Treatment of Chronic Myocarditis

This should be that described for Chronic Non-valvular Heart Disease

PART II

CHRONIC NON VALVULAR HEART DISEASE (INCLUDING HYPERTENSIVE HEART DISEASE)

Definition - The term chronic non valvular heart disease is used when myocardial insufficiency with or without the presence of myocarditis, has developed progressively in the absence of lesions of heart valves or pericardium Myocardial insufficiency and myocarditis have been defined in Part I of this chapter

Terminology

The term chronic non-valvular heart disease of the numerous ones suggested has seemed to me to be the most satisfactory one To me there is no objection to separating out a special group, patients with antecedent, recognized hypertension, and calling these cases of hypertensive heart disease However I prefer to speak of these as cases of chronic non valvular heart disease with hypertension this puts emphasis on the fact that clinically there is very little if any significant difference in these patients whether there has been or has not been demonstrable hypertension a fact which to me seems very definite Numerous physicians fail to recognize that there is a group of patients of considerable size with the symptoms and physical signs of progressing cardiac insufficiency without evidence of disease of valve or pericardium in whom no hypertension has been demonstrated some of these physicians believe that these patients have had hypertension to cause the cardiac condition but a hypertension which has disappeared prior to any medical observations made on these patients they assume preceding hypertension because clinically such patients behave just as do those who have had demonstrable continuing hypertension they consider almost all of these patients as having hypertensive heart disease I see no justification for such assumptions Numerous of these patients have been followed by me over long periods of time and there never was any hypertension

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Treatment of Chronic Myocarditis

This should be that described for Chronic Non-valvular Heart Disease

factory term for one group of these patients but, as already stated I prefer to use the term chronic non valvular heart disease for the group and then subdivide the group into two subgroups 1) hypertensive and 2) non hypertensive

Incidence of Chronic Non-valvular Heart Disease

This is the form of heart disease having the greatest total incidence among adults In children cases occur but they are relatively infrequent In childhood rheumatic or chronic valvular heart disease greatly preponderates but this preponderance steadily decreases in earlier adult age, and at about 45 chronic valvular and non valvular heart disease become of about equal incidence After that age chronic non valvular heart disease steadily increases its incidence in relation to chronic valvular heart disease to become in the older age periods the form of chronic heart disease seen most frequently In a pediatric clinic chronic non valvular heart disease would be infrequent, in contrast to this in an adult medical clinic chronic non-valvular heart disease would preponderate At the Peter Bent Brigham Hospital in Boston, where patients younger than twelve are not admitted to the medical service they formed 65 4 per cent of the 748 patients admitted to the wards suffering from chronic heart disease [4] As the result of his studies Cabot states that 77 per cent of all heart disease is due to simple hypertrophy or dilatation of the heart (or hypertensive cardiovascular disease) without valve lesions [5] Figures for the incidence of chronic non valvular in contrast to chronic valvular heart disease would vary in different parts of the country in accordance with the relative local incidence of rheumatic fever and in different clinics with variations in the proportion of patients in each age group Where rheumatic fever is relatively infrequent as in the South in the U S A, non valvular heart disease would have a higher incidence than in the North, where the converse is true With the present trend of increase in the number of old patients being admitted to the medical wards of our hospitals a further increased incidence of chronic non valvular heart disease can be anticipated beyond the 65 to 75 per cent now encountered generally in adult medical clinics At the Peter Bent Brigham Hospital Monroe in a study of 7 941 consecutive patients over 60 years of age found that 4 451 showed evidences of heart disease Of these 4 043 or 90 8 per cent were considered to be cases of chronic non valvular heart disease while 117 were diagnosed

Other terms that have been used for this group of patients include cardiosclerosis chronic myocarditis, arteriosclerotic heart disease, senile heart, cardiac hypertrophy and dilatation, chronic myocarditis, chronic cardiac myopathy, chronic myocardial disease, chronic myocardial insufficiency hypertensive heart disease Some of these terms are undesirable because they are too inclusive, others because they are not inclusive enough Some are undesirable because they imply a pathological lesion which in many of the patients is not present Cardiosclerosis is used by some to imply a diffuse connective tissue increase in the heart but this is of too infrequent occurrence to be the name for the group, for these particular patients chronic myocarditis seems a preferable term Chronic myocarditis is an unsatisfactory term for the group, because in so many of them no or only trivial chronic myocarditis is found Some use cardiosclerosis to mean arteriosclerosis of the arteries of the heart but in many of these hearts arteriosclerosis is slight or absent in the coronary arteries Arteriosclerotic heart disease is a term used by many for these patients but, as already stated, often arteriosclerosis is not present to cause the form of heart disease which these patients have The present author would limit the term arteriosclerotic heart disease to those patients in whom there is clinical or electrocardiographic evidence of disease of the coronary arteries, but even for these he prefers such terms as angina pectoris coronary obstruction and myocardial infarction, *very many of the patients with coronary artery disease do not* show symptoms and signs of cardiac decompensation or show them only very late in the course of their disease Senile heart is unsatisfactory for many of these patients are not senile and many senile patients have normal sized or even small hearts without symptoms or signs of cardiac decompensation Cardiac hypertrophy and dilatation is an unsatisfactory term for this group of cases because it does not exclude other varieties of heart disease, notably chronic valvular heart disease and congenital heart disease, it is too inclusive Chronic myocardial disease chronic cardiac myopathy, chronic myocardosis and chronic myocardial insufficiency can be regarded as terms synonymous with chronic non-valvular heart disease and be so used if the clinician prefers to do so Myocardosis was introduced to express the idea of degenerative rather than inflammatory disease of the heart muscle, a situation analogous to the use of nephrosis in contrast to nephritis but the original etymology of the term does not make it satisfactory to express this idea, nothing seems to have been gained from introduction of the term myocardosis and it is not in any general use Hypertensive heart disease is a satis-

range this increased vulnerability of the older heart causes the hearts to react in the same way to blood pressure as the hearts of the younger age group react to actually high blood pressure The patients who with hyperthyroidism or with myxedema show cardiac insufficiency, usually are in this older age group The same seems true for thiamin deficiency the beriberi heart Even numerous patients with long standing valvular heart lesions often maintain cardiac efficiency into this same age period and then become decompensated with great rapidity, this is notably true of the calcific form of aortic stenosis

Whatever the cause of chronic non valvular heart disease symptoms physical signs and progression are very much the same except that patients whose hearts show well marked fibrosis true chronic myocarditis seem to progress downward more rapidly than those without this type of lesion

Pathology and Pathological Physiology of Chronic Non valvular Heart Disease[0 3 97]

At autopsy very often the hearts of these patients appear to be unusually large, powerful organs of normal color and muscle texture They weigh more than normal with very few exceptions and usually very considerably more Cardiac chambers are enlarged with their walls thickened The ratio of wall thickness to size of the chamber the one or the other preponderating, determines whether hypertrophy or dilatation of the heart is dominant in each heart In some hearts thickening of the wall is more marked on one side than the other while in other hearts on both sides thickening has developed in the same ratio Most frequently if there is a one sided dominance of hypertrophy it is of the left ventricle and to a less degree of the left auricle This is particularly found in patients who have had hypertension In a smaller group there is right sided dominance of hypertrophy This happens particularly in patients with various lung lesions What has just been said of hypertrophy applies also to dilatation However not very infrequently it is not possible to give an explanation of the location of the dominant hypertrophy and/or dilatation in patients with chronic non valvular heart disease For example there is a curious small group of patients which recently have been reported on by Rosenbaum[9] under the title right ventricular and right auricular hypertrophy of obscure origin When we can not give a satisfying explanation for the presence of cardiac hypertrophy the term idiopathic cardiac hypertrophy is used

syphilitic heart disease, 259 rheumatic heart disease and 3- other types of heart disease

Etiology of Chronic Non-Valvular Heart Disease

Ultimate cause of chronic non-valvular heart disease largely is unknown When hypertension has existed, as it has in about three fourths of these patients, we are several steps closer to a known etiology of the heart lesion, but unfortunately of the etiology of hypertension our knowledge is slight Heredity is an important factor in its etiology, but how it causes the hypertension is not known Disturbed nervous mechanisms are important in the causation of hypertension, as is shown by the good results from various types of operations on the sympathetic nervous system Even with the existence of antecedent hypertension the immediate cause of the development of chronic non-valvular heart is not clear Coronary artery disease is a factor in causation of some cases, but in the presence of hypertension the arteriosclerotic lesions in the coronary system may be the result of the hypertension as is considered to be true of arteriosclerotic lesions in the peripheral arteries of hypertensives In a small group of patients with chronic non valvular heart disease myocarditis is causative but as discussed in the section on chronic myocarditis the etiology of only a few of these is known In a moderately large group of these patients chronic pulmonary disease particularly emphysema of the lungs is causative some of these represent chronic cor pulmonale but more often left ventricular failure is as prominent as in patients with chronic non-valvular heart disease without chronic pulmonary disease Among other occasional etiological factors for this group of patients we find thyrotoxicosis myxedema, beriberi syphilis amyloidosis arteriovenous aneurism glycogen disease of the heart etc

With all of these enumerated possible causes there remains a considerable group in which none of these causes are demonstrable[70 to 3]

On account of the high incidence of this type of heart disease, it would seem almost as if the heart in the later periods of life has for some undetermined reason an increased vulnerability to damaging influences which is lacking in the younger periods of life There are several things which suggest this Even with hypertension, which occurs frequently in this same age group it seems as if the hearts of the older patients are less able to carry on efficiently against the resistance of a high blood pressure Possibly with blood pressures within the normal

dying at the Peter Bent Brigham Hospital Boston of cardiac failure from chronic non valvular heart disease at that time termed chronic myocarditis Fitzhugh[6] found on microscopic study fibrosis of moderate degree in 4 3 per cent of marked degree in 13 per cent while 6 7 per cent showed no or only slight fibrosis He found also in this group of patients arteriosclerotic thickening of larger coronary arteries as follows, none in 11 4 per cent slight in 20 6 per cent moderate in 21 6 per cent and marked in 46 4 per cent and in small coronary branches as follows none in 19 per cent slight in 34 per cent moderate in 27 per cent and marked in 0 per cent A striking feature of these studies of Fitzhugh is the very considerable number of these hypertrophied hearts with no slight or moderate fibrosis and/or no or only slight thickening of coronary arteries

These various pathological lesions except hypertrophy and dilatation of the heart do not occur in degree and frequency to justify considering them of prime causative importance in the development of this form of heart disease There often appears to be no definite relationship between fibrosis and lesions of the coronaries nor between heart size and these lesions

The change from normal in the hypertrophied hearts of chronic nonvalvular heart disease which is of perhaps the greatest significance in the mechanism of eventual cardiac insufficiency is one that was assumed from a priori reasoning before it could be demonstrated (Christian)[18] This concerns the relation of nutrient capillaries to muscle cells As the heart increases in size the increase in size is caused mainly by hypertrophy of the individual muscle cells Except in hearts of the very young little or no increase in the number of muscle cells takes place as hearts hypertrophy The heart of normal size has one or two capillaries to each muscle cell each lying in close apposition to it As the heart hypertrophies there is almost no increase in the number of these capillaries so that in a section of heart muscle the ratio of capillary to muscle cell remains unchanged whatever the size of the heart Consequently as the fibers become larger during cardiac hypertrophy there are found fewer nutrient capillaries in each square millimeter of myocardium Wearn and his associates[9,10] have shown this relationship by making counts of capillaries after a technic was perfected for complete injection of the capillary system of the myocardium The result of this is that the larger and heavier the heart becomes the less effective in a nutritional sense becomes its blood supply

What is the mechanism or pathological physiology in cases of

A considerable number of patients with the clinical diagnosis, chronic nonvalvular heart disease, deserve the term idiopathic cardiac hypertrophy inasmuch as the cause can not be definitely placed However do not conclude that there has been any paucity of suggested etiological hypotheses for these cases, Rosenbaum[9] has tabulated from the literature 39 of them

In some patients a diffuse or focal, paler than normal grayish color suggests connective tissue proliferation, a condition of chronic myocarditis Rarely one of these hearts shows the yellowish color of fatty infiltration or degeneration Endocardium and pericardium appear normal in many of these patients, but in some there are mill patches on the pericardium or the valves and chorda tendineae are moderately thickened With dilatation of the cardiac cavities valve orifices become dilated and functionally incompetent as can be demonstrated at autopsy In many of the hearts coronary arteries are normal or show only slight lesions of arteriosclerotic nature In some of these hearts coronary artery disease is quite marked and in a few actual obstruction of a coronary branch can be demonstrated If cases with symptoms and signs of coronary artery disease are included obviously a large percentage will show marked arteriosclerotic lesions with obstruction in the coronary arteries

In hearts in which obstruction of a large coronary artery branch is found, the myocardium with this blood supply may show considerable fibrous tissue increase which changes the color of the myocardium from brownish to grayish red or the wall here may be thinned with dilatation to make an aneurism of the heart In some of these local dilatation develops to produce an aneurism of the heart

The hearts with chronic non valvular heart disease show hypertrophy and dilatation sometimes the one sometimes the other preponderating Weight is increased, many at autopsy weighing 600 grams or more while some are very large over 900 grams

Microscopic examination is confirmatory of the findings just enumerated In very many of them muscle cells show only hypertrophy with minor changes in cytoplasm and nucleus In some hearts there are fatty or hyaline muscle cells usually these are found in association with areas of connective tissue increase in these areas some muscle cells also are atrophied or have disappeared completely The connective tissue proliferation has the histological appearances already described in Part I of this chapter under the heading Pathology and Pathological Physiology of Chronic Myocarditis In a study made of 1 5 hearts of patients

Since the nucleus most probably has a very important role in the contraction of the muscle cells and requires for its normal nutrition and function substances reaching it across the cytoplasm from the capillary at the periphery of the muscle cell these substances must pass through more cytoplasm in the hypertrophied muscle cell than in the unhypertrophied one This is another probable causal factor in lessening efficiency of the hypertrophied myocardium

From the preceding it is easy to understand how and why hypertrophied myocardium has a decreasing efficiency as the hypertrophy increases With decreasing efficiency more dilatation results. In an effort to balance further the factors of decreasing efficiency, further hypertrophy is stimulated with further increase in size of muscle cells This results in a vicious cycle of dilatation and hypertrophy with a resultant decreasing efficiency of myocardium until a stage of cardiac insufficiency is reached one at first responding to appropriate therapy *but later no longer so responding Cardiac hypertrophy once started is apt to progress and in so doing become in itself a cause of serious* cardiac decompensation

Much of the change in myocardial function takes place with no demonstrable change in the appearance of cytoplasm and nucleoplasm so that at death the hypertrophied heart that has failed to function during life may appear normal under the microscope except for increased size of muscle cells However, there may be demonstrable changes as already described in this section

If arteriosclerotic lesions of the coronary arteries lessens their blood flow, obviously this accentuates the element of decreased capillary nutrition to the muscle fibers already discussed If connective tissue increases about the muscle cells, this mechanically can hinder nutrition from capillary to muscle fiber and become another factor in lessening efficiency Connective tissue in larger amount between groups of muscle cells probably also hinders the efficiency of their contraction If any substance brought to the muscle cells causes degenerative changes in them, a further factor of lessened muscle efficiency has become effective If blood pressure in the pulmonary or systemic circulation is increased an added resistance to systolic output is introduced to accelerate the changes already discussed This is true of anything causing increased resistance in the peripheral circulation

From the preceding discussion eventual decrease in myocardial efficiency and final cardiac decompensation in the hypertrophied heart is

chronic non-valvular heart disease of cardiac hypertrophy with eventual cardiac insufficiency? Cardiac hypertrophy seems a physiological sequence to dilatation of a cardiac cavity, the latter caused by increased resistance to systolic output or by need for an increased systolic output. Dilatation precedes hypertrophy. Dilatation increases the amount of blood in a heart cavity for systolic output, systolic output increases under these circumstances up to the point at which systole ceases to empty fully the blood accumulated during diastole, then systolic output begins to decrease from its maximum. As a cardiac cavity dilates its wall decreases in thickness. Beyond a certain stage of this the heart wall will become so proportionately thinned and consequently so weakened as to lessen its systolic efficiency. Before this happens a stimulus to hypertrophy becomes effective and the now thickened wall, which results from hypertrophy, again functions effectively. However as muscle cells during hypertrophy increase both in their diameter and in their length, the latter introduces a further element of dilatation with a further element of stimulation to hypertrophy. If dilatation becomes in excess of hypertrophy systolic output begins to decrease proportionately and cardiac insufficiency begins to develop. Up to a certain stage this is a reversible process and as the need for dilatation lessens dilatation decreases and such hypertrophy as has taken place disappears. The heart has returned to its normal size, now it is neither dilated nor hypertrophied. When this does not happen, a vicious cycle of recurring or progressing dilatation followed by hypertrophy is instituted. As hypertrophy progresses and becomes considerable, the enlarging muscle cells receive a decreasing nutrient supply because increase in the number of capillaries between the muscle cells does not take place. When heart muscle contracts in systole and relaxes in diastole a cycle of chemical changes takes place, a cycle from which an adequate supply of oxygen is necessary. As the hypertrophying heart has a decreasing capillary blood supply the chemical cycle in contraction and relaxation must take place with a lessened supply of oxygen and so become less complete. The supply of other substances needed in the metabolism of muscle cells, substances which are brought to the muscle cells by the capillary system like the oxygen supply, for the same reasons decreases as hypertrophy of myocardium takes place. In the same way waste products of metabolism of contracting myocardium are removed less rapidly from the hypertrophied heart because of the proportionately lessened capillary blood supply to the enlarged muscle cells and their accumulation is deleterious to cardiac efficiency.

Past History in Chronic Non-valvular Heart Disease

As to cause of this type of cardiac failure as has already been stated there is no certainty Hence past history in reference to etiology is of no positive diagnostic help Finding evidence of antecedent hypertension is suggestive evidence for this type of cardiac disease because a very considerably larger per cent of these cases have hypertension than do other forms of cardiac disease O Hare and Walker[81] have shown that an existent or antecedent hypertension with great frequency causes visible changes in the retinal arteries with or without hemorrhages and white spots in the retina In so far as this ophthalmoscopic finding points to an antecedent but no longer existent hypertension it is of suggestive help in diagnosis of this type of cardiac disease Altnow[8] has extended these observations of O Hare while working with him These views of O Hare have received confirmation in the observations of Corwin and Herrick[83] that following pregnancy a large per cent 61 per cent of these women show changes in the retinal arteries, of those whose blood pressure during pregnancy was 170 or over 77 per cent in the follow up showed retinal artery changes although only 67 per cent showed hypertension At any rate examination with the ophthalmoscope is worth while as it gives direct evidence of changes in one group of small blood vessels and we have very few means of direct inspection or indirect study of the smaller vessels of the vascular system Knowledge of disturbances in the vascular field of the retina suggests at least that there may be a more widespread disturbance of a vascular nature which may play an important role in the causation of this particular type of cardiac disturbance

Absence of Rheumatic History —History with regard to rheumatism is of help in diagnosis An absence of history of rheumatic fever in a patient with symptoms or signs of heart disease renders very improbable a diagnosis of valvular disease and strengthens the probability of there being myocardial disease Conversely a previous history of rheumatic fever minimizes the probability of only a myocardial lesion and makes very probable the existence of a valvular lesion This latter seems a surprising fact because it is believed generally that the rheumatic virus affects both valves and heart muscle certainly Aschoff bodies often are found in the myocardium of those dying in the more active stages of rheumatic heart disease Also it is generally taught that rheumatism works its damage on the heart in two ways (1) by deforming the valves and causing a mechanical burden to the circulation and (2) by injuring

understandable If we accept the idea as already suggested, that increased size of the heart is detrimental, a process that inherently will grow worse as time goes on by reason of increasingly poorer nutrition to heart muscle cells, we still lack an initiating cause, what started this detrimental process of dilatation and hypertrophy?

It would seem that possibly at some time some sort of strain has developed when the heart was susceptible to dilatation The animal experiments of Eyster and associates and of Herrmann indicate that this mechanism can institute the process and that, once started, it may continue in the vicious cycle already postulated In man a situation of this kind seems to appear in the acute failure of the aortic valve seen in syphilitic aortitis which causes an acute dilatation of the left ventricle followed by hypertrophy and subsequent cycles of dilatation and hypertrophy with *eventual cardiac decompensation A somewhat similar* occurrence may be postulated in hypertension assuming an abrupt great rise in blood pressure Usually with hypertension there is a gradual process of cardiac dilatation and hypertrophy, and for a long time the heart functions normally then in a short time rapid increase in heart size appears and cardiac insufficiency follows relatively soon Apparently abruptly a greater rise in blood pressure puts a dilating strain on the heart muscle, or the heart muscle itself quickly weakens and dilates In febrile conditions acute changes as already described for acute and subacute myocarditis may appear in the heart muscle and initiate cardiac dilatation, or toxins as diphtheria toxin, may injure heart muscle so that dilatation follows However, in the great majority of patients with chronic non valvular heart disease those with hypertension possibly excepted, it must be confessed that history and clinical examination only rarely demonstrates an acute cardiac strain to initiate the vicious cycle of dilatation and hypertrophy, and so cardiac strain may only be postulated However clinical study of patients with chronic non valvular heart disease does show that cardiac enlargement usually progresses slowly and reaches considerable degree before symptoms and signs of cardiac insufficiency appear, and then they progress rapidly The very great frequency, with which cardiac insufficiency awaits a considerable hypertrophy of the heart, emphasizes the importance of muscle cell size in the mechanism of the development of cardiac insufficiency in chronic non-valvular heart disease In many patients a heart weight of 500 to 600 grams seems to mark the point at which symptoms and signs of cardiac insufficiency begin

nea and still although showing evident signs of decompensation was reacting well to appropriate cardiac therapy

Not infrequently respiration in these patients becomes irregular or there may be a true *Cheyne Stokes type of respiration* Irregularity of respiratory rhythm is much more apt to make its appearance during sleep With few exceptions at least sometime during the course of this form of heart disease especially during its later course Cheyne Stokes respiration does occur, may be very disturbing to the patient and is of evil prognostic omen

In all of these patients it is dyspnea rather than tachypnea that occurs Respiratory rate is increased as a rule but very rapid respiration tachypnea is an exception Rarely *paroxysmal tachypnea* does appear

Always is it important to recognize that the dyspnea observed in the patient with heart dyspnea is not necessarily a symptom of heart disease The dyspnea may be due to bronchial asthma to pulmonary emphysema to bronchitis to pleurisy to pneumonia to pulmonary fibrosis any of which may be present in the patient with chronic non valvular heart disease as the prime cause of the patient's dyspnea or to accentuate the dyspnea which is being caused by the cardiac insufficiency Recognition of these various possible causative factors of dyspnea is important to the most effective therapeutic management of the patient[81]

Cough—Cough often is an annoying symptom in this form of heart disease Usually the cough is caused partly by cardiac insufficiency partly by bronchitis and pulmonary emphysema In the latter form it may long antedate cardiac insufficiency even antedate any abnormality of the heart Very interesting clinically is the patient with at first recurring bronchitis often in the form of a winter cold which gradually increases in duration and severity with increasing physical signs of emphysema of the lungs and increasing dyspnea and cyanosis who finally develops the various symptoms and signs of cardiac insufficiency This forms a quite definite group of patients with chronic non valvular heart disease those seemingly caused by pulmonary emphysema with bronchitis Cough if it keeps the patient from sound sleep and often it does just this is an added burden to a heart already beginning to decompensate Paroxysms of cough as often occur keep patients from restful sleep and make a serious drain on general physical as well as cardiac reserve

Sputum—With cough usually there is sputum sometime slight and mucoid sometimes more abundant and mucopurulent sometimes watery foamy and abundant as in pulmonary edema With repeated hard

the heart muscle in a way to interfere sooner or later, with its function One would suppose that under these circumstances not infrequently the heart muscle would be injured without valve involvement, and we would have fairly frequent cases of rheumatic myocardial disease, but such does not seem to be the case

Symptoms and Signs of Chronic Non valvular Heart Disease

Patients with chronic non valvular heart disease have symptoms and signs very similar to those found in other forms of progressing chronic heart disease particularly those with chronic valvular heart disease

Breathlessness or Dyspnea—Breathlessness or dyspnea occurs in practically all of these patients sometimes early sometimes late in the clinical progress of the case At first it is usually evident only after considerable exertion, as time goes on less and less exertion is needed to cause breathlessness finally it is present without exertion worse on lying flat orthopnea, than when sitting propped up in bed or in a chair, dyspnea now has become continuous This progress of the patient's dyspnea may be slow or rapid treatment slows its progression and lessens its severity for a varying time finally therapy no longer prevents dyspnea

The majority of patients have periods of severe dyspnea interposed with longer periods of no, or slight breathlessness These periods of severe dyspnea often develop abruptly especially at night a *paroxysmal* or *nocturnal dyspnea*, often called *cardiac asthma*, for the attack may resemble closely bronchial asthma In fact in its causation there is an element of bronchial spasm[81 85] When paroxysmal dyspnea develops in a patient otherwise seemingly free of other symptoms or signs of cardiac insufficiency its cardiac cause may fail of recognition The occurrence of paroxysmal dyspnea in itself should suggest the possibility of the existence of non valvular heart disease a possibility much enhanced in the presence of hypertension, for this form of dyspnea is less frequent in other forms of chronic heart disease with the exception of syphilitic aortic insufficiency

The attacks of paroxysmal dyspnea may be mild or severe the latter often accompanied by pulmonary edema and the attack may be fatal After its development patients usually do not live very long but this is by no means invariably true, I have seen a patient who for full 18 years had been having occasional attacks seemingly of paroxysmal dysp

nea and still, although showing evident signs of decompensation, was reacting well to appropriate cardiac therapy

Not infrequently respiration in these patients becomes irregular or there may be a true *Cheyne Stokes type of respiration* Irregularity of respiratory rhythm is much more apt to make its appearance during sleep With few exceptions at least sometime during the course of this form of heart disease especially during its later course Cheyne Stokes respiration does occur may be very disturbing to the patient and is of evil prognostic omen

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coughing the sputum may be blood streal ed, sometimes there is frank hemoptysis Sputum in cases of long continuance of cardiac insufficiency may have a brownish yellow color and contain cells carrying yellowish pigment so called *heart failure cells*

Edema —Edema is another sign of chronic non valvular heart disease and it may play an important part in its symptomatology In most patients edema first appears during the day in the feet and ankles to disappear over night Then it persists increases in amount and rises higher in the legs With persisting edema the soft pitting type changes to a somewhat, or markedly brawny type with thickening reddening and desquamaton of the skin In some cases of chronic non valvular heart disease the edema is a very prominent feature with patients becoming truly waterlogged With marked edema of the subcutaneous tissue usually hydrothorax and ascites appear and may become very marked Not very infrequently edema is such a prominent feature in these patients that its cause in cardiac insufficiency is overlooked and the patient considered to be one of renal edema with the nephrotic syndrome This is particularly apt to occur when cardiac rhythm is regular, the pulse is only moderately accelerated cardiac size is difficult of determination by physical examination, and the urine is decreased in amount and contains considerable albumin numerous casts and a few red blood cells this is a syndrome really not infrequent and often misinterpreted In these patients digitalis and diuretics as a rule produce an enormous diuresis with marked fall in body weight, sometimes they cause marked weight loss without any appreciable diuresis In some patients digitalis alone will be as effective as both digitalis and a diuretic An interesting fact is that a given patient may repeat this edema syndrome with marked diuretic response each time his heart suffers decompensation However clinical study and postmortem examination has failed to give me any clue as to why certain patients so behave, in other respects they seem just like patients with no such tendency to excessive edema In teaching I have termed these patients the good diureser type' of chronic non valvular heart disease and have enjoyed saying to house officers and students that soon Mr —or Mrs — for they seem of about equal frequency in each sex will be back with the same picture of marked edema again to recede with digitalis and a diuretic usually this is just what happens unless the patient at home is continued on digitalis and diuretic drugs in adequate dosage properly spaced

Cyanosis —In the course of their disease cyanosis of some degree almost always appears Usually it is present when dyspnea is marked

but there are patients with chronic non valvular heart disease in which deep cyanosis is the most striking feature of their cardiac insufficiency This may recur with each period of cardiac dyspnea It seems the habit of some of these patients just as marked recurrent edema is the habit of others In some of these the coexistent pulmonary emphysema and bronchitis is responsible for this marked cyanosis In others this is not the explanation and just why they develop so dark a cyanosis is not evident Otherwise they appear just like other patients of this group in whom cyanosis is not marked I have seen a careful postmortem examination fail to explain it With continued cyanosis moderate *polycythemia* may develop In some of these patients the blood shows a high CO combining figure but they do not have acidosis as this feature might suggest

Jaundice and Cachexia—With chronic passive congestion of the liver in these patients jaundice often appears usually slight but sometimes quite marked Also jaundice appears with the absorption of blood in infarcted areas in the lung With long continued insufficiency some patients lose subcutaneous fat markedly and in those parts of the body free from edema show slight to marked emaciation These patients often develop a pale sallow brownish yellow color giving the appearance of cachexia This may be enhanced by anemia which develops in some of them in part due to poor renal function and by an element of jaundice

Precordial Discomfort and Palpitation—In many of these patients precordial discomfort is complained of It is more or less continuous definitely unlike the discomfort of angina pectoris With it there may be precordial hyperesthesia and tenderness particularly in the region of the apex of the heart Of course these patients can have true angina pectoris or coronary occlusion as complication caused by an accompanying lesion of the coronaries

Abdominal Symptoms and Signs—In many of these patients abdominal symptoms are prominent and they may appear early A feeling of distension of the abdomen is common often accompanied by a tendency to belch or to pass flatus or both this is uncomfortable to the patient who seeks relief by loosening clothes about the abdomen In a few this discomfort is most prominent soon after a meal In many of the patients the upper right quadrant of the abdomen is tender to pressure and/or may be painful Liver enlargement is the usual cause Sometimes these features are so prominent as to lead to the diagnosis of cholecystitis or cholelithiasis while the cardiac disturbance is overlooked These patients may lose appetite or have nausea Constipation is frequent

coughing the sputum may be blood streaked, sometimes there is frank hemoptysis Sputum in cases of long continuance of cardiac insufficiency may have a brownish yellow color and contain cells carrying yellowish pigment, so-called *heart failure cells*

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As cardiac efficiency increases these patients return to a urine more normal than during cardiac decompensation i e the urine of the pre-existing chronic Bright's disease, their urine, however, does not become normal

Fever and Leucocytosis—When decompensation becomes marked in patients with chronic non valvular heart disease fever and leucocytosis can be expected Both decrease rapidly with proper bed rest and digitalis When first seen these patients may be thought to have bacterial endocarditis but this actually is a rare complication of chronic non valvular heart disease Since decompensated cardiac patients often show by x ray areas of increased density in the lung and since on physical examination areas of increased dullness changed breath sounds and rales can be made out when there is fever and leucocytosis, often the diagnosis of pneumonia or pulmonary infarction is made, to the former patients at present a sulfonamide or penicillin often is given unnecessarily, possibly even harmfully The latter harmfulness applies especially to sulfonamide therapy

Size of Heart—Physical examination shows with few exceptions an enlarged heart as the most significant departure from normal As a rule this can be made out by palpation percussion and auscultation In obese patients particularly women in those with emphysematous lungs and in some patients with thoracic deformity palpation percussion and auscultation do not yield sufficiently good evidence of heart size and one is forced to utilize the x-ray With them the x ray tube should be at about seven foot distance to give an approximately accurate measurement of heart size Fortunately however for all clinical purposes in most patients simple palpation and percussion give all needed information as to heart size

Slighter degrees of enlargement, not detectable by simple means of physical examination are rarely of any particular clinical significance and slight increases in heart size from examination to examination such as cannot be determined accurately by physical examination play no role in ordinary clinical work Consequently in most cases one can dispense with x ray measurements of heart size without in any way giving to your patient a less efficient service although for greater accuracy no other method of examination can supplant x ray methods either orthodiagrams teleoroentgenograms or teleofluoroscopy when intelligently interpreted Probably for clinical purposes measurement on the x ray film taken at a distance of five feet of the transverse diameter of

occasionally diarrhea occurs, but this is unusual Rarely one of these patients in apparently good compensation will pass a blood-containing stool, with chronic passive congestion of the mucosa of the intestine during times of cardiac decompensation blood in any amount from only enough to give positive reactions with guaiac or benzidine to an amount to make a tarry stool may be present

Fatigue and Sleeplessness—Fatigue, sometimes very marked, is an evidence of cardiac insufficiency not generally recognized It may be a presenting symptom in some of these patients It is not due to anemia for most of these patients are not anemic

Poor sleep at night is another symptom not generally recognized as an evidence of cardiac insufficiency It is a restlessness probably representing a summation of the various discomforts already described, no one of which is very prominent I have seen these patients after a day or two of digitalis therapy again sleep soundly almost as if they had been given a bedtime sedative Of course the dyspneic patient is apt to have sleepless hours Some of these dyspneic patients fall asleep soon to be awakened by developing Cheyne-Stokes respiration In some patients a little too much of a sedative will increase Cheyne Stokes respiration and actually disturb sleep

Urine—As the heart decreases in efficiency urine increases in concentration and deepens in color specific gravity increases, albumin casts and red blood cells appear and increase, and renal function as measured by various tests decreases Casts may be hyaline or finely or coarsely granular As heart function improves these changes in the urine recede In some patients with chronic non valvular heart disease frank hematuria may develop, this occurs most often in those with hypertension At times these urinary changes are the first signs of an impending break in compensation It is to be remembered that as so many of the patients with chronic non valvular heart disease are in the older age groups they often have kidneys with various forms of degenerative and vascular lesions, in other words, have various degrees of chronic Bright's disease they may excrete urine of lowered specific gravity with traces of albumin and scattered casts when in a stage of cardiac compensation In them as the heart becomes increasingly insufficient, the tendency of the latter to increase specific gravity and deepen color of the urine is complicated by the preexisting tendency in the other direction with a resultant compromise of renal function giving a urine intermediate between the two as to specific gravity and color but with more albumin and casts than in the urine from uncomplicated circulatory insufficiency

in those advanced stages of chronic myocardial disease in which diagnosis is no longer in doubt However even in very advanced stages it is often very striking how nearly normal in quality and intensity remain the sounds Faint heart sounds may result from weakened myocardium from an increase in the overlying pulmonary tissue from a thick chest wall muscle or fat and from unusual shape of the thorax as other than weakened myocardium are the more frequent causes, decreased intensity of heart sounds have very little diagnostic import Alone they never justify a positive diagnosis of cardiac disease

Gallop rhythm suggests weakened myocardium but little is gained by an attempt to differentiate types of gallop rhythm as presystolic gallop proto-diastolic gallop reduplication of first or second sounds embryocardia etc I myself have never gained much knowledge of heart function or help in diagnosis from observing and noting these changes and I have abandoned any attempt at recording other than the occurrence of these in a very striking degree

Murmurs—In much the same way murmurs play very little part in diagnosis of chronic myocardial disease The most important thing to know is that with very marked degrees of cardiac failure there may be no murmurs at all Frequently I have seen serious heart disease not diagnosed because of absence of murmurs The American physician still seems so obsessed by the idea of the importance of murmurs that it is difficult for him to admit of cardiac failure without murmurs and equally difficult for him to recognize that an anatomically normal heart may show a systolic murmur

Often over the heart of patients with chronic myocardial disease systolic murmurs are heard They may be heard at apex or base be soft or harsh faint or loud transmitted to axilla or up the sternum to the neck Their presence points to no special feature of the condition From the point of view of diagnosis and treatment they may be neglected entirely Their transmission as to direction and extent are only factors of their intensity and location Frequently noted they have led to the diagnosis of mitral insufficiency in these patients but organic mitral insufficiency not antecedent to or accompanying mitral stenosis is such a rarity that one is justified in saying that the diagnosis of pure or uncomplicated mitral insufficiency is incorrect almost always and practically never should be made When the heart is normal in size as so often is the case a diagnosis of mitral insufficiency may be most unfortunate in its consequences to the patient's attitude on life and its activities

In some of these patients particularly in those with hypertension

the heart, used in conjunction with the height-weight prediction tables, gives results closely approximating accuracy with simplicity of technic[95]

The important thing, however, is to know whether or not the heart is enlarged rather than its exact size So far as my experience has gone, neither diagnosis nor treatment has ever hinged on the determinaton of slight departures of the heart from normal size

So far as dilatation versus hypertrophy is concerned I have never seen any gain from an attempt to make a distinction Whenever the heart is enlarged, in a clinical sense both hypertrophy and dilatation are present One may assume that increasing signs of cardiac failure are associated with an increasing preponderance of dilatation over hypertrophy However, there is little real evidence for such an assumption One very striking thing is that cardiac enlargement very infrequently waxes and wanes in a way to suggest a considerable degree of dilatation that is recovered from It almost seems true that once enlarged, the heart of myocardial disease remains enlarged, and that enlargement after it begins progresses without regressions The myxedema heart, if such really exists, the beriberi heart and the cardiac enlargement of of arteriovenous aneurysm are exceptions to this rule, since these are seen to regress markedly in size under proper treatment Even the heart of hypertension may, following sympathectomy recede in size

If the statements in the previous paragraph are true, then dilatation apart from its association with hypertrophy, plays little part in cardiac disease This has been my clinical experience A quite consistent search for evidence of so-called acute dilatation of the heart as a cause of cardiac failure has failed to reveal examples apart from slighter degrees of dilatation accompanying tachycardia That it does not occur I would not assert, but I have not seen it among my patients

In some few patients in this group one finds no demonstrable evidence of cardiac enlargement Muscle failure seems to have taken place without muscle hypertrophy and without demonstrable dilatation One is tempted in such cases to make a diagnosis of fibrous myocarditis or coronary artery disease on the basis that there must be something demonstrable to interfere with myocardial function There does seem to be a greater probability of these in this group of hearts when there is normal or slightly increased size, but this finding is far from constant

Heart Sounds—Naturally one might suppose that in myocardial disease there would be changes in heart sounds of great diagnostic importance As a matter of fact this is not the case There are changes to be made out in the heart sounds, but these often are only present

paroxysmal tachycardia very probably is hyperthyroidism If the rate is rapid, and there is an irregularity of rhythm auricular fibrillation is the type found most frequently

This group of patients very often shows some type of arrhythmia Auricular fibrillation is the most important form, extrasystoles occur with greater frequency but are not of great clinical significance Auricular flutter heart block and other forms of arrhythmia are found but are much less frequent Incidence of course varies with frequency of observation for at times an arrhythmia is inconstant Again figures depend somewhat on how near to the fatal outcome observations are recorded for auricular fibrillation may appear only very late in the course of the disease It is to be recognized however that patients may maintain an entirely normal rhythm throughout the course of their disease, and even the electrocardiogram may fail to show any abnormality other than one indicating muscle preponderance left or right

If the electrocardiogram is used in studying these cases the form of the ventricular complex is of importance Its distortion with widening of the interval between up and down stroke notching and thickening of the stroke shortening of the height of the ventricular deflection low voltage and inversion of the T wave are changes indicative of a serious disturbance of the heart muscle certain types of curve point to blocking of the right or left branch of the bundle of His others indicate an arborization block which is much more common than block of the main branch of the bundle When these changes in the ventricular complex are found they indicate a poor prognosis However exception to this are common enough to make it unwise to base prognosis on the electrocardiogram alone Finding such disturbances in the ventricular complex does not justify more than a probable diagnosis of fibrous myocarditis, because they occur when autopsy reveals no organic lesion of the heart muscle

Of all the arrhythmias ventricular tachycardia and fibrillation are the most serious The former occurs but rarely and hardly can be diagnosed definitely without electrocardiogram, although a probable diagnosis can be made when a tachycardia occurs which on careful observation is found to show a slight variation in the time intervals between systoles in contrast to an auricular tachycardia in which the intervals between successive beats is completely regular so far as the palpating finger is concerned Ventricular fibrillation is very infrequent

a slight presystolic thrill and a late diastolic roll, rumble or murmur, usually crescendo in type, are present There is considerable discussion as to whether this thrill and murmur are identical in time and quality with the murmur of mitral stenosis Many think it is not, but I must confess my inability to distinguish by the stethoscope the difference in most of the cases In these cases usually I have found no mitral stenosis at autopsy, hence, detecting such thrill and murmur in this type of patient does not justify for me a diagnosis of mitral stenosis This type of murmur usually comes when the heart is working vigorously, although there may be evident signs of cardiac decompensation Actually this type of thrill and murmur rarely makes any difficulty in diagnosis, if the possibility of their occurrence is recognized

In many of these patients, especially in the later stages of those with high blood pressure, a low pitched blowing type of early diastolic murmur is heard at the base It begins just after the second sound and often is short Usually it is heard best just at the left sternal margin at the level of the third interspace, sometimes it is heard in the aortic or pulmonic area, occasionally it is heard over a wider area in the usual distribution of the diastolic murmur of aortic insufficiency At times it may be prolonged well through diastole This murmur by some is regarded as the Graham Steell murmur of relative pulmonic insufficiency To me always it has seemed more probable that it represented a slight leak at the aortic valve due to dilatation of that orifice At autopsy in these patients usually I have not found evidence of any organic lesions of either aortic or pulmonic cusps or adjacent areas of the aorta or the pulmonary artery

The very striking thing about all of these cases is, with few exceptions the normality of all the heart valves when seen at autopsy whether during life these patients have or have not shown murmurs of any sort

Cardiac Rate and Rhythm—With cardiac failure usually there is tachycardia but until the very advanced stages it is only tachycardia on exertion Tachycardia at rest, except in advanced heart failure is unusual except when there is an underlying hyperthyroidism or a definite form of arrhythmia or both A very rapid heart rate at rest is suggestive of some of these rather than of a simple heart failure Particularly important is that type of patient with chronic myocardial disease who, when water-logged from cardiac decompensation, has slight or no tachycardia and normal cardiac rhythm because so often these findings lead to the mistaken diagnosis of chronic nephritis and a treatment consequently incorrect A rapid rate with regular rhythm, if not

function As many of these patients have high blood pressure, the pulse usually is of increased tension As so many of these patients are elderly the arteries frequently show the changes of arteriosclerosis although marked arteriosclerosis of peripheral vessels is not particularly common with chronic myocardial disease

The most significant finding in the pulse is *pulsus alternans* If carefully searched for it will not be infrequent in the later stages of the disease When found it is indicative of a poor prognosis It may be constant or appear only following an extrasystole The latter type is of less evil prognosis If it disappears following digitalis therapy as it often does its prognostic indication is less bad than if this fails to happen Sometimes it may be detected by the palpating finger, usually then it is marked More often it can be detected while taking the blood pressure by the auscultatory method, as the pressure falls, it will be noted that at a certain level only half the beats make a sound while at a slightly lower level all are heard Very often it will be revealed only in an arteriogram made with some form of polygraph To bring out the alternation tracings may have to be made with the cuff of the sphygmomanometer on and adjusted at different levels of pressure below the systolic blood pressure It is an interesting fact that at times one of these three methods may detect a pulsus alternans missed by the other two the palpating finger occasionally in this sense may be the most delicate instrument In my experience this has been in patients with hypertension A trained finger sometimes can detect such changes when they are entirely missed by the less skilled There is enough of value to make out in feeling the pulse to justify giving a good deal of attention to this part of physical examination The older generation most assuredly did get much valuable information from feeling their patients' pulses more than I fancy those of the present generation do because we have allowed instrumental methods to replace older non-instrumental ones instead of using instrumental methods to supplement non instrumental and particularly have we failed to train ourselves in a very skillful use of the non instrumental

Diagnosis of Chronic Non valvular Heart Disease

Diagnosis is relatively simple As a rule symptoms and physical signs make it evident that the patient has cardiac disease Enlargement of the heart always indicates some form of heart disease If evidences of cardiac

unless it is the actual cause of death in cardiac lesions with sudden exitus as many believe Only the electrocardiogram will give the diagnosis

Heart block in its various forms partial or complete occurs fairly often so that it is of some clinical importance Heart block with Adams Stokes syndrome although very infrequent gives a very striking clinical picture as described in the chapter on certain forms of arrhythmia (see Chapter XIV of this volume)

The electrocardiogram very frequently shows variation in the direction of the greatest amplitude of the ventricular complexes, which from their direction in the several leads indicate right- or left sided muscle preponderence The preponderance usually is left-sided, occasionally right-sided, sometime in very large hearts there is little departure from normal curves occasionally the departure is marked, when the heart is but little enlarged None of these changes are of any special clinical importance in this group of patients

For these patients the electrocardiograph has its chief importance in detecting disturbances in the form of the ventricular complex which, as already described, may be of significance in prognosis These changes often can be recognized only by means of the electrocardiograph, except in thin patients with well marked apex impulse in whom intraventricular block often can be detected by inspection and palpation by observing the asymmetry of time of contraction of the two ventricles Actually this asymmetry is a considerable exaggeration of a difference in timing between right and left ventricles which exists in normal man when studied by a combination of fluoroscope a photoelectric pick up unit, a screen with a slot and an electrocardiograph[96, 105, 108]

An important value of electrocardiograms in this group of patients is in the checking up of diagnosis of types of arrhythmia as made by feeling the pulse and the recognition of those occasional types of arrhythmia which can be detected with certainty only by its use The actual help from the electrocardiogram in the diagnosis and treatment of this group of cardiac patients although not very great is enough to justify having them made as often as is possible On the other hand the well-trained clinician, especially he who has had familiarity with electrocardiography can diagnose and treat this group of patients with possibly a rare exception entirely satisfactorily without the use of electrocardiograms

Pulse —Disturbances of rhythm have been discussed already The size and form of the pulse are of little clinical importance in these patients As a rule the pulse gives very unsatisfactory evidence of heart

ciency but do not tell whether or not myocardial fibrosis exists The same may be said of certain of the arrhythmias especially auricular fibrillation which occurs frequently in this type of cardiac disease Paroxysmal or recurring auricular fibrillation should suggest the possibility of a complicating hyperthyroidism and lead to a determination of basal metabolism in seeking confirmatory evidence of the suspicion

If either a definitely increased or decreased basal metabolic rate is found in these patients and especially if there are other although slight evidences of thyroid disease one is justified in believing that thyroid disease has been a factor and if this idea is followed up by appropriate treatment very striking improvement in the cardiac disability may be brought about

In the same way it is important to determine the occurrence of an antecedent syphilitic infection Here history, Wassermann reaction and neurological signs are of great diagnostic help

Prognosis in Chronic Nonvalvular Heart Disease

Prognosis should not be too gloomy in this group of cardiac patients Myocardial disease occurs oftenest in the fifth and sixth decades a time when a let up in activities is desirable anyway With cardiac disability more readjustment of physical activity and greater lessening of worries are indicated If carried out these changes will make possible a reasonably long span of life except in those patients in whom symptoms are increasing steadily in severity, where peripheral vascular disease is marked or there is considerable renal insufficiency Even in those patients with marked evidences of cardiac decompensation response to treatment often is most satisfactory and under proper limitations to activity these patients may lead useful lives of considerable duration

Prognosis is to be determined in the main on a basis of a clinical estimate of the severity of symptoms and their rate of increase and the extent of the cardiac damage as determined by abnormal physical signs Certain special observations give evidence of an especially bad prognosis Vascular lesions in the retina, as observed with the ophthalmoscope help greatly in estimating the seriousness of accompanying peripheral vascular disease Tests of renal function give a measure of the part being played by the kidneys Pulsus alternans means a poor prognosis as does such changes in the electrocardiogram as low voltage depressed T waves and abnormal ventricular complexes A continued

insufficiency appear after the age of 40, the probability that the heart disease is of chronic non-valvular type is very great Hypertension increases the probability The absence of murmurs or the presence of only a systolic murmur, heard loudest in the apex region, excludes mitral or tricuspid stenosis and aortic or pulmonic insufficiency Organic tricuspid insufficiency unaccompanied by stenosis, is so exceedingly rare as to be a negligible factor in diagnosis Organic mitral insufficiency may be suggested by the systolic murmur, but without a history of rheumatic fever it occurs so infrequently as to need no consideration in diagnosis, when a satisfactory history has given no suggestion of rheumatic fever In elderly people a history of painful joints, really due to some form of subacute or chronic arthritis, may be mistaken for a history of rheumatic fever, but it is to be remembered that both rheumatic fever and rheumatic forms of cardiac disease are rare after fifty and very infrequent after forty Without a history of rheumatic fever the probability that the heart disease is of the non valvular type is very great The basal diastolic murmur in some patients with hypertension as well as the slight presystolic thrill and murmur in certain hypertrophied hearts with hypertension has been referred to already, if their occurrence in patients with chronic myocarditis or chronic myocardial failure is kept in mind, it is not likely that a mistaken diagnosis of organic aortic insufficiency or mitral stenosis will be made

In a considerable number of patients of this group there occurs dilatation of the first portion of the aorta, the result either of arteriosclerosis or of hypertension, and this causes a systolic murmur in the aortic area, which may be suggestive of aortic stenosis However, in the absence of a definite aortic thrill and a slow, small plateau type of pulse it is safe not to diagnose aortic stenosis but to consider the murmur as originating in the aorta rather than caused by a stenosed aortic valve X-ray will demonstrate the dilatation of the aorta and offers indirect evidence against aortic stenosis However, it may show calcification in or behind the aortic cusps and confirm the diagnosis of aortic stenosis of calcific type If a long diastolic murmur accompanies the basal systolic murmur this strongly indicates an organic aortic valve lesion or syphilitic aortitis with aortic insufficiency in either event a condition not belonging in the clinical group here under discussion

Certain changes in the electrocardiogram such as a distorted ventricular complex, low R and S waves depressed or inverted T waves especially when present in more than one lead, increase the probability of the diagnosis of chronic myocarditis or chronic myocardial insuffi

weel ly and to reduce food intal e whenever weight increases unless developing edema is causing weight gain In a reduction diet it is impor tant that it contain all essential foods including optimum levels of vita mins a somewhat higher than the stated daily requirement of thiamin is important for these patients since thiamin deficiency is a sometime cause of non valvular heart disease

In about three fourths of patients with chronic non valvular heart disease *hypertension* is present and has antedated the development of cardiac disease Hypertension is a serious excess load on the circulation which as the heart hypertrophies and becomes less efficient, increases in its injurious effect So treatment of hypertension as thorough as is possible is indicated for these patients This should include in properly elected cases surgical sympathectomy Surgical sympathectomy has resulted in some patients in a very striking regression of evidences of cardiac disease including decrease in heart size it has reversed what before the use of sympathectomy had been an irreversible form of heart disease The existence of the hypertensive form of chronic non valvular heart disease is a definitely important indication for sympathectomy in the management of hypertension This is discussed elsewhere in Oxford Medicine (see Ayman D Arterial hypertension, Oxford Medicine Vol II Chapter XIV F)

A *planned life* should be a part of the treatment of chronic non valvular heart disease It is wise to begin its institution early and then increase its restrictions as symptoms increase In this all excessive physi cal work or play should be interdicted Fairly active sport may be allowed to the patient intelligent enough to realize that any exercise which causes considerable breathlessness or leaves behind it marked fatigue or fatigue slowly recovered from is undesirable and should be decreased or stopped but unfortunately so many individuals lack this intelligence Competition in sports should be forbidden even in the more mildly active sports because so often the entrant even when feeling very tired will continue because he feels he or she would be a poor sport to quit A sport may be continued in if the patient has sense enough to shorten its time when undue breathlessness or fatigue results Work involving physical effort should be determined in amount and kind on the basis of the breathlessness or fatigue that results Fatigue may give a restless night and leave the patient tired in the morning this is an indication for decrease in the play or work causative of such fatigue Long hours of work even with little physical exertion should be

low vital capacity means a poorer prognosis Heart size has very little influence on prognosis, patients with hearts but little enlarged may live but a short time while one with greatly hypertrophied heart may hardly be conscious of a cardiac disability or if having some symptoms still may live for a long time

Poor coronary circulation as indicated by attacks of angina pectoris or the occurrence of cardiac infarction materially increase the likelihood of an early death

Treatment of Chronic Non-valvular Heart Disease

Treatment of chronic non-valvular heart disease should begin when the diagnosis is made rather than to await symptoms and signs of developed cardiac insufficiency but treatment should not be the same for each stage in the progression of the patient's heart disease from the period of no symptoms to that of congestive failure It is to be realized that the great majority of the patients diagnosed as having chronic non-valvular heart disease will experience this progression and eventually, unless some other cause of death intervenes will die from their heart disease Treatment however can and should prolong this progression, sometimes for many years and make much more comfortable the life, although a variously limited one of a patient with this form of heart disease So we have a somewhat paradoxical situation in which optimism is fully justified in the therapeutic management of a chronic progressive usually finally fatal disease

Treatment in the Stage of No or Very Slight Cardiac Insufficiency

At this stage treatment should be directed mainly to measures designed to lighten any excess load on the circulation To *decrease body weight* in the patient who is over-weight is a most important part of the therapeutic management designed to lessen load on the circulation This should be accomplished by a dietary regime appropriate for lessening obesity Very important is to continue restrictions in diet to prevent regaining any of the excess weight It is to be remembered that advice to decrease physical activity may be given to many patients and that the patient advised to exercise his muscles less will gain in weight unless his food intake is lessened It is important for these patients to weigh

Treatment in the Stage of Well Marked Cardiac Insufficiency or Congestive Failure

Rest and the three Ds (diet, digitalis and diuretics) are our chief therapeutic weapons when the patient develops evident cardiac insufficiency

Rest — At this stage rest is a necessity in treatment For most patients this means a period of twenty four hours in bed with as complete relaxation as is possible but it does not call for heavy sedation as is so commonly practiced today heavy sedation is undesirable if for no other reason because it contributes to development of venous thrombosi and consequent pulmonary embolism but there are other undesirable features of heavy sedation notably the dulled sensations and depressed psyche of the heavily sedated patient For the majority of well treated patients with marked cardiac insufficiency sedation is only needed to give a few nights of good sleep after that sedation is not required The cardiac patient should not begin the day with a hangover depression from the night s sedation

The *bed* for the cardiac patient should have two criteria of suitableness First it should be comfortable for the patient Second it should be of a type to facilitate nursing care These criteria are met best by the rather narrow bed which can be raised mechanically at the head end be flexed at the level of the patient s knees, is on wheels, the two at one end so arranged as to rotate from side to side and have flexible springs and a smooth, resilient mattress This bed permits easily having the patient sit propped at different levels and prevented from slipping down by the elevation of the mattress under the patient s knees With its wheels it can be turned about and moved from room to room These beds can be manipulated easily by one nurse, and she easily can reach the patient for all nursing care Its disadvantage is that the usual thin mattress on springs makes it cold for the patient when room temperature is lowered by letting in outside air as should be done for most patients from time to time often for these reasons several layers of thick wool blanket will be needed beneath the under sheet Since many cardiac patients at home will need to spend much time in bed, such a bed should be purchased for home use

How strictly should *bed regime* be required? For most decompensated patients twenty four hours in bed is best but not for all The patient who has difficulty in urination and defecation in bed and many do should be allowed to use a bedside commode the male may stand to

shortened on the same basis of produced fatigue It is wise to modify the character of the patient's work to reduce his fatigue, usually it is unwise to make the patient change completely his work or to stop it altogether, rarely a complete change of occupation or cessation of work should be advised

A part of the patient's planned life is concerned with *hours in bed and other periods of rest and relaxation* Nine to ten hours in bed each night should be insisted on The patient probably will need to learn how to sleep long hours by training himself to muscle and mental relaxation patients can do this A glass of milk or a warm bath at bedtime for some patients is conducive to relaxation and sleep A rest period after luncheon either lying down or relaxed in an easy chair with the patient guarded against interruptions is desirable For many men the after-luncheon cigar or pipe conduces to relaxation Cigarettes are not so restful Women need to be taught how to relax, sewing and knitting scarcely are in the category of relaxation

In the planned life the *patient's psychology* needs to be considered For many the desired goal must be arrived at by gradations Advice that unduly irks the patient is not the wisest way of procedure Understanding and cooperation may have to be reached gradually Compromise may be far more effective than insistence This is all the more reason for beginning a planned life early in the patient's development of symptoms and signs of heart disease

Judicious use of *sedatives* in the early stages of chronic non valvular heart disease may be necessary for some patients but for very many patients sedation will not be needed Except for possible sedatives and digitalis as described in the next paragraph no drugs are required in these early stages of heart disease

Digitalis in continuation dosage has been advised when hypertrophy of the heart has begun[86] As already pointed out, cardiac hypertrophy seems a process harmful rather than beneficial Certainly when it becomes marked it has seemed harmful There is evidence from animal experiments to indicate that digitalis can act to decrease heart hypertrophy and delay cardiac insufficiency For this reason I[86] have advocated giving digitalis continuously even before any definite evidence of cardiac insufficiency appears, and this practice has seemed to me to be a desirable prophylactic therapy to delay cardiac insufficiency The dosage should be that described later for continuation therapy with digitalis

carefully to detect first signs of venous thrombosis If this is detected today many advise heparin or dicumarin to prolong clotting time of the blood Others advise prompt ligation of the saphenous vein at groin level to block emboli from going to the lungs Even if an infarct already has developed in the lungs one or the other of these procedures should be carried out My own preference has been for vein ligation in these patients However it is to be recognized that the problem of thrombosis and embolism is much more extensive than one of leg localization and that much improvement is being brought into the technic of using anti coagulants[99, 100, 101] so that this view of mine is one probably not fully justified at present With such prophylaxis embolism will be a less frequent and less serious complication of cardiac disease

Diet —For the first few days never more than seven of treatment of a patient with cardiac edema the Karell diet of 800 c c of milk divided into 4 feedings is admirable After that any easily digestible food may be given divided into four feedings, many prefer to make up the needed calories with an excess of carbohydrates while others prefer more protein and fat with less carbohydrate A low calorie value 800 to 1 000 is desirable so long as cardiac insufficiency is of a degree making continuance of bed life as already described seem needed When the patient begins out of bed physical activity calorie increase is desirable always having in mind that the cardiac patient should not put on weight and that the diet should be rich in vitamins and not be made up to any great extent of bulky items of low calorie value

Sodium chloride should be restricted and when edema is present greatly restricted, the patient then receiving a diet that is as nearly sodium chloride free as is possible i e with sodium chloride down to 1½ to gm a day[88] The following low sodium diet has been suggested[107]

LOW SODIUM DIET

Food Allowed

1 Meat boiled fish or poultry prepared and served without salt
2 Egg—one daily
3 Milk—limited to glasses (1 pint)
4 Vegetables—(as desired) any fresh or frozen vegetables except lima beans prepared and served without salt
Fruits—(as desired) fresh canned stewed
6 Breads—only yeast bread prepared without salt

urinate and often this is very important for older men These procedures may be distinctly less of a strain on the heart than the in bed struggle to urinate and/or defecate In an occasional patient compulsory bed treatment increases dyspnea and even may precipitate pulmonary edema[8] Such patients do better at these times, if allowed to sit in a comfortably arranged chair instead of being in bed because this lessens the amount of blood to enter the right auricle from the legs and so lessens the blood which may accumulate in the lungs, when left ventricular failure has not improved proportionately, with the result that the right heart delivers blood faster than the left can take care of Some as Levine[8] advise raising the head end of the bed by placing under the legs of the bed at the head end blocks of wood 8 to 9 inches high for such patients The observant physician and the intelligent patient carefully listened to can work out for the individual patient the desirable exceptions to the general rule of twenty-four hours in bed for decompensated cardiacs

Patients with chronic non valvular heart disease like other cardiacs in the stage of marked insufficiency have a considerable incidence of embolism from either mural thrombi in the heart or thrombi in the peripheral veins, especially those in the legs The emboli from the heart may go either to the lungs or to the viscera supplied by the peripheral arterial system while those from the peripheral veins go to the lungs Emboli will produce symptoms and signs dependent on what organs they land in and the size of the emboli Pulmonary embolism with either sudden death or infarction of the lungs is most frequent of these in incidence Little can be done to prevent embolism from mural thrombi in the heart, but much can be accomplished in prophylaxis against thrombosis of leg veins and consequent embolism to the lungs It seems to me that heavy sedation, so commonly practiced at the present time in the management of cardiac patients is an important causative factor in the formation of thrombi in leg veins because it makes for increased stagnation of blood in them by reducing to a minimum change of body position and movement of the legs of these patients Consequently I advise against heavy sedation for cardiac patients Also I think the cardiac patient should be encouraged to make frequent changes of position in bed and to move his legs about The nurse can help in the former by periodically turning the patient from side to side Long periods on the bed pan is conducive to stagnation in the leg veins and must be avoided Short periods out of bed if cardiac insufficiency is not too great, often is advisable Patient s legs should be inspected often and

11 Avoid dried fruits, such as figs, dates, raisins apricots, and prunes
12 Avoid lima beans fresh or dried
13 Sodium containing medicines such as soda bicarbonate soda mints tums alka-seltzer, and various indigestion powders should not be used Salt gargles and toothpastes containing sodium likewise are forbidden

Recipe for Salt Free Bread

6½ lbs bread flour
10 oz sugar
8 oz shortening (Primox)
4 oz yeast
2 qt water

This makes six loaves Apparently this bread takes a little longer to rise than ordinary bread

It is the sodium that needs restriction and so be certain that the patient in his therapy at this time is receiving no sodium salt, such as sodium bicarbonate sodium bromide, etc

Fluid intake needs no or only slight restriction when the patient is on the diet very low in sodium chloride otherwise a total fluid of not more than 1,800 to 2 000 c c should be the rule increased in hot weather or if the patient for any reason sweats The former practice of great restriction in fluid-intake caused unneeded discomfort, so often these patients actually were dehydrated Even with marked edema dehydration was present as shown by dry, parched lips tongue and throat and a dry skin where edema was not present to conceal it Uncomfortable thirst should not be allowed to continue If the sodium chloride in the diet is kept very low the patient can take as much fluid as is needed to satisfy his thirst without increasing his edema If the patient is mentally sluggish or very weak, as often is the case, fluid should be given by the nurse at regular periods in measured amount

Care of Bowels —Vigorous catharsis, formerly advised particularly as a means of removing excess body fluid no longer is advised The patient with cardiac insufficiency needs a mild cathartic or an enema in just the same way as do other patients, i e, to prevent disturbing constipation When the diet as often it is for these patients is low in residue a daily bowel movement by mild cathartic or enema is not needed The abdominal distention not infrequent in cardiac patients rarely is caused by constipation a thought useful in the management of these patients

7 Cereals—any cooked cereal prepared without salt The only dry prepared cereals allowed are puffed rice, puffed wheat, shredded wheat and Muffets'
8 Potatoes and rice prepared without salt Macaroni, spaghetti and noodles contain salt and are not to be used
9 Butter—unsalted or washed butter
10 Desserts—custards junkets, and plain puddings made with milk allowance and with no added salt, jello pies with no salt added to the crust and filling prepared with fresh or canned fruit (no meringues)
11 Beverages—tea, coffee carbonated drinks or fruit juices
12 Flavorings—cocoa, chocolate, caramel, maple, peppermint, lemon orange vanilla maraschino cherries, cloves cinnamon allspice nutmeg ginger and coffee
13 Seasonings—pepper (black or red), curry, dry mustard mint, dill vinegar parsley, paprika sage, thyme, onion, garlic, pimiento rosemary
14 Sweets—white or brown sugar honey molasses jellies, jams marmalade, or preserves which do not contain sodium benzoate

Special Instructions

1 No salt is to be used in preparation of food or in cooking or to be added to the food after it comes to the table
2 Avoid all canned foods which have salt added such as canned meats and fish, vegetables soups tomato juice and V-8 cocktail
3 Avoid all brine-cured and smoked foods such as bacon ham pickles or smoked fish meat or sausages and olives
4 Omit all salty foods, such as salted nuts, potato chips, and buttered or salted popcorn
5 The following food accessories are also to be omitted because of their salt content meat extracts and sauces, chili sauce catsup, mustard and relishes
6 Do not use any cheese clams oysters lobsters
7 Use only yeast breads prepared without salt
8 Use no foods prepared with baking soda or baking powder such as soda crackers biscuits muffins cakes and cookies
9 Use only unsalted or "washed' butter Sweet butter may have salt added so be sure to read the label before using it
10 Home-made mayonnaise may be used if prepared without salt

Digitoxin Digitaline Natuelle (digitaline crystallosee Natuelle)
basic dose 0 1 mgm by mouth
1 c c (containing 0 mgm digitoxin) intravenously
Digitalin German
basic dose 0 1 mgm by mouth
Digitalis lanata
Digilanid
basic dose 0 33 mgm by mouth
c c (containing 0 4 mgm digilanid) intravenously
Digoxin
basic dose 0 .5 mgm by mouth
1 c c (containing 0 5 mgm digoxin) intravenously
Strophanthus gratus
injectio ouabaini—ouabain injection (U S P)
basic dose 1 c c (containing 0 5 mgm ouabain) intravenously
Strophanthus Kombe
Injectio Strophanthini—strophanthin injectio (U S P)
basic dose 1 c c (containing 0 , mgm strophanthin) intravenously

As an example for the patient with well marked congestive failure not already receiving digitalis or none for 10 days previously digitalis therapy is advised using by mouth tablets pills or capsules of powdered digitalis in the following plan 0 5 gm (5 cat units) (5 times the basic dose) followed in 4 hours by 0 5 gm and followed in 4 hours by 0 , gm for the patient not yet showing signs of satisfactory response the day following this the patient is given 0 1 gm (1 basic dose) three times a day or 3 basic doses and this rate is continued until there is evidence of satisfactory response in slowing of pulse increase in urine output or loss of appetite then the dose is reduced to 0 1 gm (1 basic dose) each 4 hours if nausea develops digitalis is stopped until it disappears

For lesser degrees of congestive failure this plan can be modified in various ways In the first 24 hours 1 dose of 0 5 gm (5 basic doses) may be given followed in 4 hours by a econd dose of 0 5 gm (5 basic doses) then 0 1 gm (1 basic dose) three times in the second day with continuation as described in the preceding paragraph Another plan is to give 0 5 gm (5 basic doses) twice in the first 4 hours 1 hours between the two doses or only 0 5 gm (5 basic doses) may be given in the first 4 hours Still another plan is to begin with 0 gm (. basic

Digitalis — This is needed by practically every patient who has evidences of cardiac insufficiency[90] Its use in the stage of well marked cardiac insufficiency or cardiac decompensation will be discussed in the following paragraphs, its use in less marked insufficiency will be described later on under the heading Continuation Digitalis

The kind of digitalis preparation used is relatively unimportant, the amount given is very important and should be determined in detail by the physician in relation to the day-to day condition of the patient's circulation There are numerous digitalis preparations available, some suited only for mouth dosage, some suited only for intravenous use some suitable for either route, intramuscular and rectal dosage with digitalis preparations occasionally is desirable The digitalis preparations besides U S Pharmacopoeial ones include numerous specially named preparations When produced by reputable pharmaceutical companies these are effective forms of digitalis to be used in the same way as the U S Pharmacopoeial preparations The author is of the opinion that they have no special advantages for general use but may be used in accordance with the individual physician's preference and experience Personal preference and experience of the attending physician are important elements in the selection of the form of digitalis preparation that will be used It has seemed to the author better if the physician confines himself to the use of very few preparations of digitalis and so is thoroughly familiar with their therapeutic effectiveness

The word, digitalis is used by me to mean any preparation having an effective and usable digitalis action not preparations of digitalis purpurea alone The more important digitalis preparations in frequent use at present with their basic dosages, *basic meaning average advised once daily dosage*, may be listed as follows

Digitalis purpurea
- Digitalis pulverata powdered digitalis (U S P)
  - basic dose 0 1 gm by mouth
- Injection digitalis—digitalis injection (U S P)
  - basic dose 1 c c (containing 0 1 gm 1 cat unit, digitalis) intravenously
- Digalen digifolin, digipoten digitan and digitol are some of the preparations from digitalis purpurea made by different pharmaceutical houses with a variety of claimed advantages over U S P preparations
  - basic dose of each stated on its container

strophanthin or ouabain intravenously as already described and at the same time commence giving by mouth a preparation of digitalis purpurea or lanata at the rate of one basic dose three times a day This will have the advantage of getting a quickly appearing effect from strophanthin or ouabain which will last about 24 hours while the more slowly acting digitalis begins its effectiveness

In the experience of the author really very few patients with chronic non valvular heart disease require intravenous medication with any one of the group of drugs with digitalis action The plan for mouth dosage, which has been described has proven for him effective for the great majority of these patients When not effective it has seemed for most of them that they have reached the stage of their disease in which no form of digitalis therapy including intravenous any longer will give satisfactory results

In successful therapy with digitalis it needs to be recognized that patients do not have the same susceptibility to the drug The physician who adheres closely to any fixed formula of dosage will encounter some patients who show with it toxic manifestations and some patients who fail to give a satisfactory response For the first group the formula of dosage contains too much digitalis for the last group too little digitalis For these reasons the patient receiving digitalis needs careful supervision until the physician finds out what his patient s susceptibility to digitalis is When this has been recognized any formula of dosage in accord with this can be followed through with results that usually will be satis factory The author believes that there is too great a tendency among practitioners to give digitalis too much by rule and too little on the basis of intelligent careful observation Even those specializing in cardiology do not seem always undeserving of this criticism

Quinidine —The use of quinidine is appropriate if an arrhythmia amenable to it, occurs and is disturbing Auricular fibrillation is of frequent occurrence in patients with chronic non valvular heart disease but usually it appears late in the course of the disease and is not influenced very effectively by quinidine For the great majority of these patients quinidine should not be given, I have had occasion to use it only very infrequently in chronic non valvular heart disease since digitalis usually controls the heart rate and under these circumstances auricular fibrillation is little disturbing to the patient

Diuretics —For some cardiac patients with the edema of congestive failure digitalis alone is an effective diuretic For many others one of the other diuretic drugs is needed in addition to digitalis The diuretic

doses) repeated in 3 doses each 24 hours or even 0 1 gm (1 basic dose) three times in each 24 hours Obviously many combinations can be used Interestingly for each patient a particular plan selected on the basis of knowledge of the degree of the patient s circulatory deficiency, may work out better than another one The experienced observant physician treats increasingly well his cardiac patients when he does not become too routinely wedded to a single plan of procedure

Treatment by mouth dosage with other of the digitalis preparations already enumerated, can be planned by substituting in the preceding paragraphs the same multiples of the basic dose by mouth of any one of them and proceeding on the same principles, except that with digitoxin or digitaline Nativelle by reason of its more rapid and more complete absorption from the stomach, fewer basic doses in all probability will be required particularly as concerns the earlier doses

It is to be remembered that digitoxin or digitaline Nativelle digitaline and digoxin have a potency 1 000 times as great as powdered digitalis and so need to be watched very closely for toxic reactions Failure to do this with the increasing use of these stronger preparations has resulted already in an increased frequency of digitalis intoxication[108]

For the patient who already has been receiving digitalis the dosage just described should be reduced in ratio to the digitalis already given and the severity of the patient s decompensation

For the nauseated or vomiting patient or the very ill patient with marked cardiac decompensation, not previously receiving digitalis in stead of the earlier relatively large mouth dosage intravenous therapy should be substituted using 5 basic doses of digitalis purpurea or digitalis lanata preparations in form suitable for intravenous use once or twice in the first 24 hour period and then 1 or 2 basic doses every 24 hours until the patient s condition justifies using digitalis preparations by mouth Instead of these preparations ouabain or strophanthin may be used giving intravenously 1 basic dose each 24 hours rarely basic doses at 1 hour intervals in the first 24 hours This difference in plan of treatment is based on the possibly quicker action of the last drugs and the much shorter duration of their action For intravenous dosage I prefer them to preparations from digitalis purpurea or digitalis lanata and of the two I prefer strophanthin to ouabain as it is less toxic

When using any drug of the digitalis group by intravenous route greater caution must be used for patients previously having received digitalis by mouth as the danger from digitalis intoxication is greater

A plan useful at times for badly decompensated patients is to give

Xanthine diuretics are available also They have the advantage of effectiveness when given by mouth and they can be given more comfortably at more frequent intervals than the mercurial diuretics with dosage planned so as to produce a more prolonged and continuing diuresis This is desirable when it can be accomplished In my experience often xanthine diuretics have given excellent results in the edema stages of chronic non valvular heart disease and have advantages over the mercurial diuretics including the absence of the occasional serious even fatal toxicity of the latter when given intravenously I believe that they should be used more frequently

In this group of xanthine diuretics I have obtained satisfactory results with theobromine and sodium acetate (diuretin) theocalcin (mixture of calcium theobromine and calcium salicylate) theophylline (theocin) theophylline and sodium acetate (soluble theocin) all in U S Pharmacopoeia except theocalcin The average dose of theobromine preparations is 0 5 gm (gr 7½) once a day and of theophylline ones 0 2 (gr 3) once a day In general the theophylline drugs are more effective than the theobromines but more apt to cause nausea Theophylline ethylene diamine (aminophylline) also is a diuretic but in my experience not giving so active a diuresis as the others just described

Urea in large doses 60 to 90 gm per day is for an occasional patient a satisfactory diuretic Its advantage is that it may be given daily to produce a continuing diuresis Its disadvantage is that for most patients it is very unpalatable its disagreeable taste can be modified by taking it in tomato or fruit juice

Ammonium chloride and *calcium chloride* occasionally for some patients are satisfactory diuretic drugs to be given daily over long periods of time

All diuretics should be given in time relations so as to produce the maximum diuresis during daylight hours so as to hinder night sleep as little as possible This can be determined for each patient by observing the time interval between giving the diuretic and the period at which urination becomes most frequent

Mechanical Removal of Fluid — Ascites in these patients usually is controlled by diuretic drugs If not removal by abdominal thoracentesis is advisable Hydrothorax is not as a rule satisfactorily controlled by diuretics If present in amount sufficient to embarrass respiration mechanical removal of pleural fluid accumulation by thoracentesis is advised and this should be done promptly and repeated as often as the hydrothorax returns to embarrass respiration For the patient seen with

may be given after digitalis has had time to produce some of its effects or it may be commenced when digitalis is begun If there is marked edema, the latter is preferable Increasingly diuretics particularly the mercurials are being given along with digitalis is the preferred plan of treatment

Of the diuretics one of the mercurials is the most effective but not necessarily and always the most advantageous one to use The mercurials should be given intravenously or intramuscularly The usual dose for this for patients with considerable edema is 1 to 2 c c of the solution as dispensed for parenteral use With intravenous dosage it is advisable if there is no cause for great haste to bring about diuresis to give a test dose of ½ c c the day before the therapeutic dose to find out if the patient has any special susceptibility as infrequently is the case For many patients a 1 c c dose is effective, others need 2 c c, a rare patient requires 3 or even 4 c c Sometimes with many repetitions a patient gradually needs increase in the dose formerly effective At present mercurophylline (mercurophylline injection of U S P XII mercuzanthin of Campbell Products Co) and particularly, mercuhydrin of Lakeside Laboratories (meralluride of A M A New and Non-official Remedies) as they seem less irritating in intramuscular usage, seem the most satisfactory of the mercurial diuretics Some prefer mersalyl and theophyllina (solution salyrgan theophylline of Winthrop Chemical Co) All of these mercurials besides the mercury compound contain theophylline Mercurial diuretics formerly were given intravenously at weekly intervals sometimes biweekly to control the patient s edema, but increasingly and with excellent results they are being given much more frequently even daily in intramuscular dosage of 0 5 to 2 c c guiding dosage by daily weighing the patient[91] A continuous weight loss of a few pounds daily is preferable to a great diuresis with a corresponding immediate weight loss of 5 to 10 pounds

These drugs are dispensed also in tablet form for mouth dosage[9] and also in suppository form for the rectal route of dosage For some patients they are effective by these routes After trial to find out the most effective dosage mouth dosage may prove satisfactory for some ambulatory patients it does not seem a method to be recommended for bed patients

A better diuresis often is obtained if on the two days before the mercurial diuretic is given ammonium chloride, 1 to 2 gm (gr 15 to 30) is given by mouth four times a day Sometimes continuation of ammonium chloride in such dosage without any other diuretic is satisfactorily effective

of months of life remaining to these patients It is most surprising how often these months under wise guidance can be lived in comfort with the patient capable of considerable effectiveness in his chosen activities maintaining cheerfully his morale It is this which gives the physician optimism in his treatment of patients with chronic cardiac disease and not infrequently brings to him actual surprise when a patient in time and in activity goes far beyond what had been judged the probabilities of his prognosis

Continuation Digitalis —The patient after a successful treatment of his congestive failure should have a daily ration of digitalis This may need to range from 0 0 5 to 0 gm of powdered digitalis or 0 025 to 0 mgm of digitoxin once a day with a rare patient tolerating and apparently needing 0 1 gm of digitalis or 0 1 mgm of digitoxin three times a day The majority of the patients do best on 0 1 gm of digitalis or 0 1 mgm of digitoxin once a day but the optimum dosage should be determined for each patient by trial and error In my experience this has proven of great importance since the best results seemingly are obtained when the daily dose of digitalis is one just short of the amount which when continued for 2 or 3 weeks will show evidences to toxicity The method to follow is to have the patient take 0 1 gm of powdered digitalis or 0 1 mgm of digitoxin daily until some loss of appetite develops or if no loss of appetite develops to continue this dosage for a period of 3 weeks If appetite loss appears the digitalis should be discontinued for or 3 days and then given again in a little smaller dose for another trial period If in the full 3 weeks period no loss of appetite develops a somewhat larger dose should be tried out Also the weight of the patient observed at frequent intervals is an important check on the plan of treatment, since a quick rise in weight indicates that edema is developing which calls for increase in digitalis dosage or the usage in addition to the digitalis of a diuretic or for the use of both digitalis and a diuretic In this way the optimum dosage for the individual patient can be found out then used

I have seen a rare patient for whom 0 0 5 gm of powdered digitalis daily was optimum in this sense a considerable number for whom 0 05 gm daily was optimum very many for whom 0 1 gm daily was optimum and a considerable number for whom more than 0 1 daily was optimum There are numerous patients for whom the optimum dosage is between the ones just enumerated For them for example a plan should be established alternating a smaller and a larger dose as 0 05 gm one day and 0 1 gm the next or the digitalis preparation may be given every

congestive failure and marked edema with hydrothorax I always have removed the hydrothorax as one feature of the therapy given as soon as the patient is gotten in bed in a semi reclining position at the same time starting digitalis therapy and at nightfall giving 15 mgm (gr ¼) of morphine sulfate, to delay thoracentesis in these patients seems to me to be bad practice

With marked edema of the lower extremities rising to the level of the abdominal wall and greatly swelling the genitalia, if diuresis lags I have found drainage with *Southey's tubes* inserted in the skin of the top of the foot useful It is surprising how much fluid may be drained off in this way even from the high levels of its accumulation

Patients from whom much fluid is being removed whether by diuretic drugs or mechanical drainage will become dehydrated and so will need more fluid by mouth Since they are losing sodium and chloride they are in the situation of patients being managed by a diet very low in sodium chloride and so will tolerate a considerable increase in fluid intake Rarely so much sodium chloride is lost that the patient is improved by an increase in intake of this substance

Continuation Treatment After Congestive Failure Has Had Effective Therapy

Now physical activity must be arranged with care to suit the efficiency of the patient's circulation This must be judged by observing the effects of a gradually increased period out of bed followed by a gradual increase in physical exertion Much can be accomplished for the patient's physical comfort and morale by intelligent planning of his daily life with its needed rest period and long hours in bed at night A plan of continuation digitalis and diuretics optimum for the individual patient must be worked out based on the patient's weight the goal being to maintain this at the level obtained in the plan of treatment already described a weight termed by Gold and his associates the patient's "dry weight" Diet must continue to be adequate in calories and vitamins easily digestible, not bulky not excessive in carbohydrates fats or protein, in amount and content so that the patient does not get too heavy

In many respects this is the most important period of management of the patient who has undergone congestive failure with recovery from it in part or completely for this period will make up the greatest number

possible free from edema i e not gaining weight in the way most comfortable to him Frequent weighing of the patient is the most satis factory way to follow the use of diuretics If this is done the quite inconvenient measurement and recording of excreted urine may be dis pensed with, incidentally this measurement plan has possibility of so frequent errors as to make it unsatisfactory except in special services organized in nursing care beyond that of even the best general hospitals

other day or four or five days out of the week For each patient the physician by such trial and error method can arrive at the dosage most suitable to producing the best results of continuation digitalis therapy As I see it, at the present time often the best results are not being obtained even by cardiologists because of the evident tendency to give all cardiac patients not in congestive failure a routinely recommended dosage of digitalis daily in a routine way

Continuation digitalis as just described, in my opinion is desirable also for the patient with evidences of chronic non valvular heart disease who has never had congestive failure, but who has very slight evidences of cardiac insufficiency and also for the patient with enlarged heart without any symptoms of cardiac insufficiency

Continuation Diuretics —For many patients continuing or recurring edema is an unpleasant feature of otherwise rather moderate cardiac insufficiency For this the various diuretics already described may be used How to use them is a problem which must be solved for each patient by trying different diuretics with attention to using dosage to give optimum results As for continuation digitalis the method of trial and error must be applied for continuation diuretics For trial any of the diuretics described in a previous section may be used Diuretics by mouth can be tried first using ammonium chloride calcium chloride urea one of the xanthines or a mercurial Since ammonium chloride or calcium chloride must be given several times each day and for many are not very active diuretics not often do they prove satisfactory A very occasional patient can take urea in a large dose once a day and get a satisfactory diuretic effect Many more patients find a xanthine or mercurial diuretic by mouth effective usually they work best, if given every second or third day If these by mouth do not prove satisfactory a mercurial given intramuscularly or intravenously once or twice a week or more often is for most patients a satisfactorily effective diuretic and many patients have continued their usage in this way for many, many weeks guiding dosage by frequent weighings, increasing the diuretic when weight increase indicates returning edema as described on a previous page

As can be seen from the preceding statements, the physician has a considerable number of diuretics from which to choose Many variations in size of dose and in repetition and route of dosage are available Consequently many plans of treatment are available, and by trial one can be selected which suits best the individual patient The goal for using continuation diuretics is to keep the patient as constantly as is

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PART III

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CHAPTER XIII-C

THE COR PULMONALE

Including a Discussion of the Interrelations of the Heart and the Lungs

By PAUL D WHITE

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INTRODUCTION

The Interrelations of the Heart and the Lungs

One of the most common important and difficult problems that confronts the physician who deals with heart disease is that of the relationship of the heart and the lungs Anatomically they are connected

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intimately by blood vessels their surfaces are separated only by thin serous membranes the pleura and the pericardium and physiologically they are interdependent It is a common experience of the internist that diseases of the one may affect the other and that independent diseases of both are found frequently in the same person Because of their juxtaposition and of the fact that they are both intrathoracic organs with closely similar nerve connections their symptoms and signs in disease often closely resemble each other and may result in confusion and difficulty of diagnosis in fact sometimes it is impossible to distinguish disease of the one from that of the other The present chapter therefore is one of the most important considerations of either heart or lung disease

One of the most serious of all clinical disturbances of the circulation often unrecognized is pulmonary embolism with or without infarction pulmonary embolism can either simulate or complicate heart disease and itself may be complicated by secondary cardiac abnormalities Great advance has been made in its clinical recognition and pathological understanding in the last few years It is not to be confused with the cor pulmonale which is the subject of the present chapter although it may lead to it Pulmonary embolism really is a much more important condition than the cor pulmonale itself because of its extent seriousness possible prevention and treatment

Besides pulmonary embolism and infarction there are many other pulmonary conditions that may simulate or complicate heart disease for example acute respiratory infection in which râl s at the lung bases may resemble the rales of pulmonary edema and chronic bronchitis with emphysema producing dyspnea which may be mistaken for and wrongly treated as cardiac dyspnea in old persons Pneumonia still is a common ending of chronic cardiac patients continuing to serve despite the sulfonamides as the old man s friend and with or without pulmonary embolism to terminate a state of chronic cardiac invalidism It is natural for an older person to have more things wrong than in the case of a young person Hence the combination of coronary or hypertensive heart disease and chronic bronchitis or asthma is frequent just as one frequently finds digestive disorders and hiatus hernia accompanying coronary insufficiency and producing the same kind of pain although under different circumstances

Then too we have as a most important effect of the heart on the lungs vascular stasis which occurs acutely with left ventricular failure or with tachycardia complicating mitral stenosis or chronically with long standing left ventricular failure or mitral stenosis Such conditions may

cause great pulmonary vascular engorgement and encroachment by the distended blood vessels on the alveolar spaces with reduction of vital capacity There is also in many such cases edema of the parenchyma and there may be bleeding into the lungs although the latter is less common than in pulmonary infarction

Some diseases affect both heart and lungs simultaneously for example severe rheumatic fever Not only does there tend to be a pancarditis in such cases but so called rheumatic pneumonitis or pneumonia may occur There are also the interesting cases of thoracic and spinal deformity with kyphoscoliosis in which the action of both heart and lungs is interfered with giving a so called pulmonocardiac insufficiency or failure Generally in such cases pulmonary reserve is more encroached upon than cardiac reserve although eventually death from heart failure may end the story Finally the serous membranes of heart and lungs may be involved simultaneously in a chronic inflammatory process with effusion (often spoken of as polyserositis) hampering the action both of the heart and of the lungs and sometimes leading to chronic inflammatory induration and constriction producing the picture of chronic constrictive pericarditis or pleuritis

The present chapter deals primarily with the effect of lung disease on the heart that is pulmonary heart disease or the cor pulmonale and not vice versa In high degree both acutely and chronically important secondary effects of pulmonary disease on the heart are infrequent although lesser grades of strain doubtless are very common and sometimes hardly recognizable even by the pathologist at autopsy It is of great importance to distinguish symptoms and signs of the underlying and more important pulmonary disease from those of the secondary heart disease This however commonly is not done The dyspnea and cyanosis found in such cases which may be wrongly ascribed to heart failure actually are due to pulmonary insufficiency

I shall divide the discussion to follow into three groups namely acute subacute and chronic cor pulmonale the first and last of which are of greater importance

Acute Cor Pulmonale

Definition — The acute cor pulmonale is a heart whose right ventricle and often right auricle too is dilated by abrupt pulmonary hypertension secondary to massive obstruction of the pulmonary circulation most commonly in the form of pulmonary embolism very rarely other causes may exist such as marked acute diaphragmatic herniation (McGinn and Spear 1941[4])

Incidence

It is impossible to ascertain how common the acute cor pulmonale is for in slight degrees it is hard to recognize and in fact may not be diagnosed at all When it is difficult of recognition because of its slight degree it may be considered clinically unimportant In easily diagnosable form that is in moderate to high degree the acute cor pulmonale apparently is not very common It has been seen in a large hospital service or in private practice several times a year The reason why it has not been emphasized earlier or recognized more often is that knowledge of its existence clinically has been rather recent (McGinn and White 1935[1] White 1935[3])

The acute cor pulmonale is found in a rather small minority of cases of pulmonary embolism which fact of course explains some of the misunderstanding expressed in recent literature One must clearly distinguish pulmonary embolism and its effect on the electrocardiogram and other records on the one hand from the acute cor pulmonale and its effect on the other Only some 10 per cent or perhaps less of the cases of pulmonary embolism develop the acute cor pulmonale at least in recognizable form Even this of course means that a good many cases scattered through the countryside go undiagnosed We have identified recently in this clinic 10 cases of the acute cor pulmonale among 102 cases of pulmonary embolism (Murnaghan McGinn and White[5]) Gradually the condition is becoming recognized quite widely and so it will doubtless seem to be more and more common as time goes on hitherto it has been confused frequently with pulmonary embolism itself or with acute heart failure or with myocardial infarction

Etiology

Cause — The cause of the acute cor pulmonale in the great majority of cases is as stated above massive pulmonary embolism the obstructing clot almost invariably coming from one of the long leg veins secondary to a phlebothrombosis and going on to block more than 50 per cent of the *pulmonary circulation at least in the acute state at the beginning of* trouble Repeated recurrent pulmonary embolism may result in a gradual increase in the pulmonary obstruction finally to the point of producing marked pulmonary hypertension and the acute cor pulmonale no one of the emboli then need block over 50 per cent of the circulation and yet the combined blocking may be adequate to produce the picture The reasons why the condition is not seen more commonly aside from failure of recognition are doubtless due to the facts that the pulmonary embolism

itself is either not severe enough or else that it is so severe that a state of shock occurs with resulting marked reduction of the blood supply to the heart and therefore insufficient pulmonary blood pressure to dilate the right ventricle Not infrequently the embolus is large enough to block both pulmonary arteries as a rider embolus usually one artery more than the other it is also possible to have a clot break into several pieces or to have several different emboli block several major pulmonary arterial branches to cause the same effect as one large embolus

Sex — The sexes are about evenly divided In the original series of McGinn and White there were 6 males and 3 females and in this last new group of 10 cases collected by Murnaghan McGinn and White there were 4 males and 6 females

Age — The condition is much more common in middle aged and older persons quite naturally because of the incidence of pulmonary embolism in older persons whose circulation is less adequate and who are more likely to have operations or accidents which favor the laying down of clots in the leg veins The commonest age is between 50 and 70

Pathology

There is no structural change in the heart in the acute cor pulmonale except for dilatation of the right ventricle and often also of the right auricle and of the pulmonary artery and sometimes of the pulmonary and tricuspid valve rings Such dilatation is temporary and may be as a matter of fact largely an antemortem finding The heart chambers may contract down to normal heart size with recovery or at death The volume of the acute cor pulmonale is ordinarily not found to be greatly increased since the right ventricle does not make up a very large part of the heart mass to start with and since it is notoriously difficult to ascertain the presence of slight or even moderate enlargement of the right ventricle clinically

Symptoms

There are no symptoms of the acute cor pulmonale per se except perhaps for a sense of increased force and laboring of the heart s action and perhaps some distress or pain It is probable that the majority of the symptoms including distress in the chest found in cases of the acute cor pulmonale comes from the underlying pulmonary embolism and infarction these symptoms are substernal oppression pleural pain dyspnea and shock

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there is none at all because if the pulmonary circulation is good and the collaterals adequate pulmonary embolism may not lead to any pulmonary infarction at all The diaphragm tends to be unduly elevated on the affected side

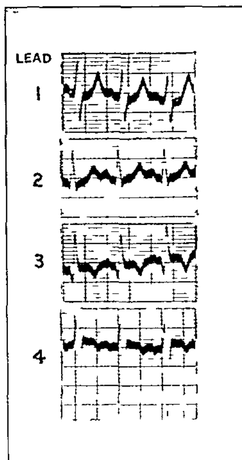


Fig 1 Electrocardiogram showing the four leads of a woman 26 years of age with an acute cor pulmonale secondary to massive and recurrent pulmonary embolism Note the prominence of the S waves in Lead 1 and of the Q waves in Lead 3 and late inversion of the T waves *in Leads 3 and 4 Also note the tachycardia at a rate of 145*

The *electrocardiogram* of the full blown acute cor pulmonale is typical and diagnostic There is a characteristic pattern (see Fig 1) This pattern consists of the appearance or considerable accentuation of S waves in Lead 1 prominence of Q waves and inversion of the T waves

Right heart failure although occasionally present as shown by distended neck veins does not often reach the stage severe enough to give rise to symptoms therefrom such as liver pain and discomfort from swollen legs inasmuch as the acute cor pulmonale tends either to subside rapidly or to go on to speedy death secondary to the pulmonary embolism

Signs

The diagnosis of the acute cor pulmonale is dependent on the signs which in the classical cases include evidence of enlargement of the right ventricle forceful pulsation of the pulmonary artery which may be palpable and visible in the second intercostal space at the left of the sternum sometimes a pulmonary systolic murmur usually marked accentuation of the pulmonary second sound sometimes superficial to and fro murmurs over the pulmonary artery that sound like and probably are due to pericardial friction (without pericarditis) the result of a distended pulmonary artery There may be enough failure of the right ventricle to cause dilatation and increased pulsation in the jugular veins The pulse tends to be rapid and regular sometimes paroxysmal tachycardia or even auricular flutter or fibrillation is induced by the pulmonary embolism whether or not the heart is dilated but usually the rhythm remains regular The blood pressure tends to be low with rather small pulse pressure secondary to the disturbed circulation higher however than in the presence of shock

Other signs except electrocardiographic are due to the underlying pulmonary infarction but may not appear for the first twenty four hours or more when they do they often include some percussion dulness at the lung bases changed breath sounds râles and not infrequently a pleural friction rub over the site of the infarct Still other clinical abnormalities at the time of the acute cor pulmonale are secondary to the pulmonary embolism or infarction These include cyanosis fever leucocytosis and blood spitting it should be noted however that the majority of cases of pulmonary embolism do not have hemoptysis

X ray examination of the lung does not help much Most patients are too sick at the time of the occurrence of the acute cor pulmonale to stand the strain of x ray study If however x ray examination is made enlargement of the right ventricle may be difficult to note unless the condition is at its height and is especially looked for in the oblique views which may show the right ventricle bulging anteriorly The x ray examination may or may not show pulmonary infarction In some cases

do recover Some become subacutely ill from the underlying pulmonary embolism especially if recurrent for weeks or months Such cases may die suddenly later on after days or weeks as the result of a new pulmonary embolus unless preventive measures are taken Rare cases go on t the chronic cor pulmonale after recovery from the immediate effects of a massive pulmonary embolism

Complications

There is no particular complication of the acute cor pulmonale except that in a few cases actual right heart failure develops with some liver enlargement in some cases arrhythmias occur usually in the form of tachycardias rarely of heart block and in a few of the older patients secondary myocardial infarction may develop

The thrombophlebitis which is mainly responsible for the underlying pulmonary embolism may be very hard to discover but it should be looked for very carefully It is not itself a complication but rather the pulmonary embolism and acute cor pulmonale are complications of it

Differential Diagnosis

The acute cor pulmonale is to be differentiated strictly from the pulmonary embolism that underlies it from myocardial infarction and from congestive heart failure with which it is frequently confused and which it may complicate or which may complicate it Enough has been said under the headings Symptoms Signs Course and Prognosis and Complications above to make the distinction usually an easy one Electrocardiographic analysis at the proper time is of prime importance in the differentiation

Treatment

Drugs — There is no particular treatment of the acute cor pulmonale beyond that of the underlying pulmonary embolism and leg phlebothrombosis other than the use of oxygen and the possible value of the administration of digitalis Morphine already will have been used routinely for the severe pulmonary embolism that has precipitated the acute cor pulmonale it is undoubtedly helpful for the heart also Oxygen inhalation by mask or tent probably is more important for the pulmonary embolism than for the heart but it should be a routine measure Atropine given with the morphine may be useful to counteract the effects of

in Lead 3 and lowering up to the point of actual inversion of the T waves in Lead 4 the routine apex precordial lead Exploration of the precordium by the special chest leads is helpful sometimes in revealing inversion of the T waves in the second and third precordial leads at which points the T waves are normally upright The abnormalities of the electrocardiogram tend to subside quickly in the course of a few hours to a few days unless the condition is long continued Hence to find this pattern it is important to obtain an electrocardiogram at the height of the clinical manifestations of the acute cor pulmonale

Other changes in the electrocardiogram are common in pulmonary embolism but not characteristic of the acute cor pulmonale they are due to temporary changes in a heart muscle already diseased for example in coronary heart disease of moderate severity the strain and anoxemia secondary to pulmonary embolism may produce or aggravate electrocardiographic evidence of coronary insufficiency Such findings should not be confused with the characteristic pattern of the acute cor pulmonale although they may complicate it Furthermore many cases with pulmonary embolism have normal electrocardiograms throughout or no change in their previously abnormal findings because there is not enough strain on the normal or abnormal heart to produce any changes

One further consideration is important with respect to the electrocardiogram and that is that the pulmonary embolism itself with or without the acute cor pulmonale may as a result of direct strain or of coincident shock produce myocardial infarction As a rule in such cases the heart already is the seat of a high degree of coronary artery disease There may then develop the typical electrocardiographic pattern of either posterior or apical myocardial infarction

Course and Prognosis

The acute cor pulmonale tends to last only a few hours or perhaps even only a few minutes prior to recovery or death In some instances already noted the condition may last for days and rarely may go on to a subacute or chronic state of pulmonary heart disease chronic cor pulmonale

During the acute cor pulmonale the clinical picture is that of a very ill patient There are weakness dyspnea cyanosis fever leukocytosis tachycardia and apprehension due essentially to the underlying pulmonary vascular block

The prognosis must be very guarded in cases of the acute cor pulmonale in fact it is often bad The majority of patients however,

do recover Some become subacutely ill from the underlying pulmonary embolism especially if recurrent for weeks or months Such cases may die suddenly later on after days or weeks as the result of a new pulmonary embolus unless preventive measures are taken Rare cases go on t the chronic cor pulmonale after recovery from the immediate effects of a massive pulmonary embolism

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unfavorable vagal reflexes both from the pulmonary embolism and from the morphine Atropine can be given with the morphine in a dosage of 0 6 mgm (gr $\frac{1}{100}$) of atropine sulphate to 15 mgm (gr $\frac{1}{4}$) of morphine sulphate Morphine and atropine may be repeated in the course of an hour or two but morphine should not be given in excess since it may depress the respiration too greatly Papaverine hydrochloride in a dosage of 30 mgm (gr $\frac{1}{2}$) subcutaneously has been recommended also as an antispasmodic and for possible effect on the coronary circulation It is doubtless less important than the morphine and oxygen If breathing stops artificial respiration should be tried, it may succeed

Nursing Care — The most careful nursing attention is vital and of at least as much importance as the use of the drugs mentioned above

Underlying Conditions — As soon as the condition of the patient permits search should be made for phlebothrombosis or thrombophlebitis in the legs it is sometimes evident on physical examination but sometimes it requires diodrast x ray study of the leg veins Since recurrent pulmonary embolism is common either after operation or after accidents or in cardiac or other medical patients during long bed rest and since pulmonary embolism practically always arises from a clot in the leg vein ligation of the leg veins especially of the long saphenous or superficial femorals preferably on both sides is indicated in the early stages after the immediate recovery from a state of shock collapse or cardiac dilatation to prevent further trouble which may end fatally, even though later emboli may be small Heparin or other anticoagulant may be used prophylactically postoperatively to reduce the incidence of pulmonary embolism and thereby the acute cor pulmonale but its administration is not in itself a sure means of avoiding serious recurrent pulmonary embolism

Preventive measures in the way of maintaining a good peripheral circulation routinely when in health and massage and early exercises of the legs as for example by bed bicycle postoperatively are of the greatest importance in cutting down the incidence of the acute cor pulmonale

Subacute Cor Pulmonale

The subacute cor pulmonale the transitional stage between the acute and the chronic is the rarest of the three groups inasmuch as the acute cases as a rule either get well entirely or quickly succumb while the great majority of the chronic cases begin very slowly and insidiously without any clear cut acute or subacute phase

The subacute cor pulmonale is represented almost invariably by an

stances of massive pulmonary embolism not serious enough to kill quickly and yet obstructing the pulmonary circulation to such a high degree that it is impossible for the heart to return to a normal state Thus there persists for weeks or months a dilatation of the right ventricle such as is found in the case of an acute cor pulmonale along with the signs thereof already enumerated in the last section Gradually the subacute cor pulmonale in the course of three to four months evolves into the chronic state except for a few cases which expire in the subacute stage either from right heart failure or more likely from recurrent pulmonary embolism Whether nonfatal severe traumatic lesions involving the thorax can produce the subacute cor pulmonale has not yet been demonstrated although such a development is conceivable

Chronic Cor Pulmonale

Definition —The chronic cor pulmonale consists of enlargement mainly hypertrophy of the right ventricle due to a chronic pulmonary hypertension secondary to a variety of pulmonary lesions and not the result of heart disease per se So far as the right ventricle itself is concerned there may be no distinction structurally between the chronic cor pulmonale and the enlarged right ventricle in cases of mitral stenosis and chronic or recurrent failure of the left ventricle but clinically the distinction is important and the term cor pulmonale should be restricted to those cases in which pulmonary hypertension is due to pulmonary disease or thoracic deformity The cor pulmonale is to be carefully distinguished from the syndrome of Ayerza per se which is a clinical state of deep cyanosis due to chronic pulmonary disease which may include endarteritis obliterans and which secondarily affects the heart

Incidence

The chronic cor pulmonale in slight degree doubtless is very common but in high degree it is rare It has been pointed out by a number of observers including Thompson and White 1936[1] and Scott and Garvin 1941[1] that slight enlargement of the right ventricle is commonly missed not only by the clinician but also by the pathologist unless at autopsy the heart is examined very carefully and the weight of the right ventricle compared with the weight of the left It may be next to impossible to determine the presence or absence of the lesser degrees of right ventricular enlargement Measurement of the thickness of the wall of the right ventricle and rough estimate of the volume of the right ventricle are very

inadequate and even these measurements often are not carried out properly For example the right ventricle may be quite dilated with an average thickness of the wall of 3 mm and yet no note made of the fact that such a ventricle is actually enlarged in such a case the weight naturally would be increased above the normal as much as if the ventricle were of average volume with a thickness of wall of 5 to 6 mm Thus at the present time the frequency of lesser grades of cor pulmonale is almost a pure guess but enough observation has been made of hearts at autopsy to know that enlargement of the right ventricle is more common than ordinarily suspected

Since these lesser grades of the chronic cor pulmonale are however not clinically important they will not be discussed at length in this chapter Only the well marked instances will be referred to Therefore cases of the chronic cor pulmonale easily recognizable either clinically or at autopsy may be estimated as making up approximately 1 per cent of the cardiac cases seen through much of the countryside particularly in the northeastern part of the United States

Etiology

Cause — The immediate cause of the chronic cor pulmonale is chronic pulmonary hypertension The underlying factors behind the pulmonary hypertension are varied but the most common of the important causes is pneumonoconiosis especially silicosis which is found usually in quarry or mine workers or in grinders of stone or even in manufacturers of gritty soap Less common of the important causes are extensive fibrosis of the lungs from widespread pulmonary infections including rare cases of tuberculosis pulmonary endarteritis obliterans usually of unknown cause, tracheal or bronchial stenosis pulmonary collapse and thoracic deformities particularly extensive kyphoscoliosis

Ordinary respiratory or pulmonary infections emphysema and asthma do not cause enough increase of the pulmonary blood pressure to produce the chronic cor pulmonale One striking case of severe and chronic asthma that I myself had followed a woman of about 60 who had had a very high degree of bronchial asthma for 35 years and had used adrenalin several times a day for at least 20 years showed at autopsy after death from pneumonia a perfectly normal heart with no enlargement of the right ventricle and perfectly smooth elastic aorta and coronary arteries However there are instances of asthma superimposed on fibrosis and of emphysema with large blebs in which there results the chronic cor pulmonale Scott and Garvin have shown that among certain populations in

particular people from southeastern Europe living in Cleveland there may be a high enough degree of pulmonary involvement from chronic infection to produce fairly frequent examples of the chronic cor pulmonale As stated above under the definition the pulmonary disease per se even with intense cyanosis as in the black cardiacs of Ayerza s syndrome must be distinguished carefully from manifestations of the chronic cor pulmonale per se This has been done so inadequately in the past that much confusion has resulted

Age — The chronic cor pulmonale is found most commonly in middle aged and old persons but in its earlier and lesser stages it is detected occasionally in relative youth particularly among those exposed to silica dust and certain of the other underlying conditions such as primary pulmonary endarteritis obliterans and kyphoscoliosis are responsible for relatively early development of the chronic cor pulmonale even in children The youngest cases I have encountered were a boy 11 years old with endarteritis obliterans and an infant 6 months old with failure of the pulmonary alveoli properly to expand after birth

Sex — The male sex is preponderantly represented in chronic cor pulmonale due in part to greater exposure to silica dust and in part to a higher incidence of other fibrotic lesions of the lungs In one series of cases the preponderance was extr m 48 to 2 (Scott and Garvin 1941) in other series the ratio was much less

Pathology

The only structural pathological finding so far as the heart is concerned in cases of the chronic cor pulmonale is enlargement of the right ventricle this consists in the main of hypertrophy In well marked cases the right ventricle may closely equal the left ventricle both in volume and in weight in fact on occasion the right ventricle may form as much of the apex of the heart as does the left ventricle (see Fig 2)

In the adult the right ventricular wall normally measures 3 mm and the weight of the right ventricle is about 70 grams These measurements may be doubled in cases of chronic cor pulmonale The pulmonary artery is dilated as a rule and the pulmonary valve may in rare cases become incompetent without being diseased Similarly the tricuspid valve may become incompetent when there develops eventual failure of the right ventricle and then the right auricle also becomes dilated and hypertrophied

inadequate and even these measurements often are not carried out properly For example the right ventricle may be quite dilated with an average thickness of the wall of 3 mm and yet no note made of the fact that such a ventricle is actually enlarged In such a case the weight naturally would be increased above the normal as much as if the ventricle were of average volume with a thickness of wall of 5 to 6 mm Thus at the present time the frequency of lesser grades of cor pulmonale is almost a pure guess but enough observation has been made of hearts at autopsy to know that enlargement of the right ventricle is more common than ordinarily suspected

Since these lesser grades of the chronic cor pulmonale are however not clinically important they will not be discussed at length in this chapter Only the well marked instances will be referred to Therefore cases of the chronic cor pulmonale easily recognizable either clinically or at autopsy may be estimated as making up approximately 1 per cent of the cardiac cases seen through much of the countryside particularly in the northeastern part of the United States

Etiology

Cause — The immediate cause of the chronic cor pulmonale is chronic pulmonary hypertension The underlying factors behind the pulmonary hypertension are varied but the most common of the important causes is pneumonoconiosis especially silicosis which is found usually in quarry or mine workers or in grinders of stone or even in manufacturers of gritty soap Less common of the important causes are extensive fibrosis of the lungs from widespread pulmonary infections including rare cases of tuberculosis pulmonary endarteritis obliterans usually of unknown cause tracheal or bronchial stenosis pulmonary collapse and thoracic deformities particularly extensive kyphoscoliosis

Ordinary respiratory or pulmonary infections emphysema and asthma do not cause enough increase of the pulmonary blood pressure to produce the chronic cor pulmonale One striking case of severe and chronic asthma that I myself had followed a woman of about 60 who had had a very high degree of bronchial asthma for 35 years and had used adrenalin several times a day for at least 20 years showed at autopsy after death from pneumonia a perfectly normal heart with no enlargement of the right ventricle and perfectly smooth elastic aorta and coronary arteries However there are instances of asthma superimposed on fibrosis and of emphysema with large blebs in which there results the chronic cor pulmonale Scott and Garvin have shown that among certain populations in

Symptoms

There are no symptoms of the chronic cor pulmonale per se until it fails and then we have the characteristic evidence of right ventricular failure in the increased systemic venous pressure with heaviness in the right hypochondrium due to congestion of the liver. The symptoms of dyspnea, cough, fever and weakness that may be found in cases of the chronic cor pulmonale are due to the primary pulmonary disease and not to the secondary heart disease.

Signs

It may be very difficult on *physical examination* to note the enlargement of the right ventricle that is present in cases of the chronic cor pulmonale. The heart may or may not be obviously enlarged. It is to be remembered that the right ventricle is an anterior chamber and so may be increased anteriorly without being very evident by physical examination. However, there does tend to be increased pulsation to the left of the lower end of the sternum and in the epigastrium and there also tends to be, with the pulmonary hypertension, a loud pulmonary systolic murmur and accentuation of the pulmonary second sound, rarely followed by a pulmonary diastolic murmur due to incompetence of the valve. When the right heart fails there is an increase in the jugular pulse in the neck and engorgement of the liver with the development eventually of edema of the dependent parts of the body.

The cyanosis that is common in cases of the chronic cor pulmonale is due primarily to the underlying lung disease, but it may be increased when the heart fails as the result of stasis in the systemic circulation. Lung signs such as râles and abnormal breath sounds are due entirely to the underlying disease of the lungs.

The pulse usually is of average rate and normal rhythm in cases of the chronic cor pulmonale. Arrhythmias are very infrequent. The blood pressure tends to be normal or low. The arm to lung circulation time tends to be normal unless there is right heart failure, but the circulation time through the lungs tends to be slowed due to the pulmonary vascular obstruction.

X-ray examination often is helpful in revealing, particularly in the oblique views, the prominence of the whole right ventricle and also of the pulmonary artery and infundibulum. The pulmonary arc may or may not be very prominent; sometimes it bulges almost as much as in the



FIG 2 Photograph of the heart from a case of chronic cor pulmonale secondary to ex tensive silicosis in a man 29 years old Note the massive thicknes of the wall of the righ ventricle which ha been opened and which forms a large portion of the apex of the heart The view looks up into the infundibulum of the right ventricle under the tricuspid valve The right auricular wall also is thick

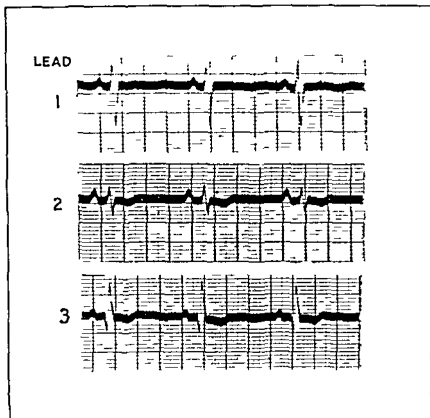


FIG 4 Electrocardiogram showing the three classical leads in a case of chronic cor pulmonale a woman aged 46 with idiopathic pulmonary fibrosis chronic cor pulmonale and right sided heart failure Note the normal rhythm at a slow rate (0) and the well marked right axis deviation

Electrocardiography is a very important method of examination in the detection of the chronic cor pulmonale Almost invariably well marked right axis deviation is present as is shown in Fig 4 Systemic hypertension or other cause for strain of the left ventricle may neutralize the evidence of right ventricular enlargement in the electrocardiogram but usually the strain is but one sided and so there is a rather characteristic pattern It is however impossible to be absolutely certain whether moderate right axis deviation in the electrocardiogram is due to a chronic cor pulmonale mitral stenosis or certain congenital heart defects



FIG 3 Roentgenogram of the thorax in a case of extensive pulmonary fibrosis and chronic cor pulmonale a man aged 49 years Note the marked increase of the lung markings and the prominence of the left upper border of the heart shadow

case of patency of the ductus arteriosus The lung vessels themselves may be more prominent than usual although not invariably so The lungs may show extensive fibrosis or silicosis An example of the characteristic x ray picture of the chronic cor pulmonale is seen in Fig 3

murmurs the prominence of the pulmonary artery the well marked but not extreme right axis deviation by electrocardiogram and usually the presence of pulmonary disease all help to establish the diagnosis of the chronic cor pulmonale in contrast to the other conditions in which murmurs of valvular disease or congenital defects marked cardiac enlargement arrhythmias and other positive findings are common However the chronic cor pulmonale remains one of the difficult types of heart disease to diagnose with assurance

Treatment

There is no treatment for the chronic cor pulmonale per se The underlying disease which has caused the pulmonary hypertension should be treated if such treatment is possible Therapy of the heart failure itself if such supervenes follows the methods routinely outlined in this volume in the chapters (Chapt XIII–A and XIII–B) on Chronic Cardiac Valvular Disease and Chronic Non valvular Cardiac Disease It may be well however to keep persons with large right ventricles even without symptoms or signs of failure on rations of digitalis 0 065 to 0 1 (gr 1 to 1½) of the dried leaf daily to support the heart and to delay or to prevent dilatation and failure of the right ventricle

The most important measures are preventive with respect to the inhalation of dust the contraction of respiratory infections including tuberculosis and the correction of chest deformities if such is possible Whether or not it will ever be feasible to clear old thrombi from the main pulmonary trunks surgically and thereby relieve the pulmonary hypertension of rare cases so affected we cannot predict if the diagnosis is clear such an attempt would seem not beyond the realm of possibility

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Course and Prognosis

The chronic cor pulmonale is usually very slow and gradual in its development with no definite time of onset. It has a prolonged course and a fairly good prognosis. In itself it rarely ends fatally, death coming as a rule from intercurrent infections, particularly involving the lungs in the form of tuberculosis or pneumonia, or from co-incident diseases or accidents.

The onset may, however, be sudden as in the uncommon cases of the acute cor pulmonale due to massive pulmonary embolism that proceed by way of the subacute cor pulmonale to the chronic stage.

The termination of life may be the result of failure of the right heart, i.e., of the cor pulmonale itself, and in rare instances death may be sudden. The average duration of life in the chronic cor pulmonale is a good many years; just how long is not known; it largely depends on the cause. In one clear-cut instance in a young man 29 years old with a high degree of the chronic cor pulmonale death came from pneumonia complicating marked silicosis 3 years after the entrance of this young man into an atmosphere containing much silica dust; there was no heart failure but autopsy showed a very large right ventricle (see Fig. 2) and massive pulmonary silicosis. Endarteritis obliterans may proceed to a fatal ending in a few years too, most likely from heart failure itself, but in some instances the course is longer and the heart does not fail. In marked chest deformities with kyphoscoliosis death usually comes in youth or middle age through respiratory failure, pulmonary infection, or, less often, congestive heart failure.

Complications

The most important complication of the chronic cor pulmonale is failure of the right ventricle. That, however, is uncommon. The pulmonary complications of the underlying pulmonary disease are much more common and serious. These include especially pneumonia and tuberculosis. Subacute bacterial endocarditis, arrhythmias, coronary insufficiency and valvular disease are notable by their absence.

Differential Diagnosis

The chief difficulties in diagnosis are in differentiating the chronic cor pulmonale from pulmonary disease, congenital heart disease, rheumatic heart conditions and neurocirculatory asthenia. The absence of heart

CHAI TER \III–D

THE PATHOGENESIS OF CONGESTIVE HEART FAILURE

By TINSLEY R HARRISON

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INTRODUCTION

Chronic cardiac disease of sufficient severity to represent an important clinical problem usually falls into one of two categories which may occur simultaneously but usually appear separately These are (1) the anginal type due to disturbances in the oxygenation of the myocardium and characterized especially by pain and (2) the congestive type due to alterations in the circulatory dynamics and fundamentally characterized by engorgement either in the pulmonary circuit (failure of the left side of the heart) in the systemic circuit (failure of the right

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1 Thyrotoxicosis
2 Constrictive pericarditis
3 Adhesive pericarditis occasionally
4 Wounds of the heart
5 Tumors of the heart rarely
6 Arteriovenous fistula
7 Certain types of congenital heart disease, more especially patent ductus arteriosus *

c Conditions not amenable to therapy
1 Most types of congenital heart disease
2 Cor pulmonale due to various conditions causing either long standing or severe obstruction to the blood flow through the lungs
3 Certain types of cardiac disease due to thiamine deficiency and accompanied by irreversible changes in the myocardium and endocardium
4 The arteritic diseases including periarteritis disseminated lupus and possibly, scleroderma
5 Various rare diseases including trichiniasis sarcoidosis amyloidosis glycogen storage disease xanthomatoses etc

Aggravating Causes of Heart Disease (the precipitating causes of heart failure) — Although progress is being made in the prevention of rheumatic fever and although there is reason to believe that better methods of treatment of this disease and of hypertension may be available in the near future it is still true that in the majority of patients with heart disease of the congestive type the underlying cause cannot be prevented or treated successfully Hence proper attention to the aggravating causes which usually can be avoided or managed successfully is a matter of the greatest importance The most important of these conditions which tend to precipitate heart failure in a patient already suffering from heart disease are

1 Acute infections especially those of the respiratory tract
2 Excessive exertion
3 Cough
4 Pregnancy
5 Obesity
6 Changes in the cardiac rhythm more particularly auricular fibrillation
7 Anemia
8 Emotional stress

The stages of cardiac disease Although complete recovery from chronic

* Succes ful operations also have been reported this year on con enital pulmon c ten o is[43] and on coarctation of the aorta[44] (H A C.)

side of the heart) o in both of these areas (the combined type of congestive failure) This chapter will deal only with the second of these types of chronic heart disease

The problem of congestive heart failure can be understood best if one has a clear conception of (1) the etiological factors, (2) the clinical course and (3) the pathological physiology It is with the third aspect of the problem that we are primarily concerned here nevertheless a brief summary of the first two aspects which have been covered in more detail in other chapters, may not be out of place

Causative Factors of Congestive Heart Failure — Two types of agents need to be considered (a) the underlying factors which produce heart disease but which acting alone rarely produce heart failure and (b) the aggravating factors i e, conditions which, acting on a normal subject, will not usually affect the heart but which affecting an individual already afflicted with heart disease tend to aggravate the progress of the disorder and to precipitate congestive failure

Underlying Causes of Heart Disease — These may be divided conveniently into (1) those which are very common and (2) those which are less common the latter being further subdivided into those which are specifically amenable to surgical therapy those which are specifically amenable to medical therapy and those which tend to be refractory to all therapy According to such a classification the underlying etiological factors may be tabulated somewhat as follows

A The very common causes of chronic cardiac disease of the congestive type
  1 The senile heart (presbycardia) *
  2 Hypertension
  3 Rheumatic fever
B The less common causes of chronic heart disease
  a Conditions specifically amenable to medical treatment
    1 The beri beri heart (certain types)
    2 Thyrotoxicosis
    3 Severe anemia
    4 Myxedema
    5 Syphilis †
    6 Diphtheria †
    7 Bacterial endocarditis
  b Conditions specifically amenable to surgical therapy

* This is usually spoken of as arteriosclerotic heart disease However the recent report of Dock (1) points toward the conclusion that arterio clerosis plays a relatively small role in the production of this disorder which is to be ascribed mainly to senile changes in the myocardium itself rather than in the arteries which supply it Many of the older clinicians and apparently correctly also had the view that arteriosclerosis in itself did not cause heart disease in the sense of dilatation and hypertrophy with cardiac insufficiency (H A C)

† These diseases are amenable to therapy in their earlier stages Once they have attacked the heart pecific therapy has relatively little to offer

ure if not present, is impending These include (1) dilatation of the heart of considerable degree ( ) gallop rhythm and (3) persistent auricular fibrillation The latter condition will not be discussed as it is thoroughly considered in another chapter in Oxford Medicine To discuss cardiac enlargement in detail would lead us too far afield The reader is referred to the fundamental reports of Starling [*] and to the publications of Christian[4] and of Harrison[5 6 7] for discussion of the relationship between enlargement and failure of the heart

Gallop Rhythm —When one or both ventricles are dilated the amount of residual blood remaining in these cavities at the end of systole is increased Hence during the rapid phases of diastolic filling the limits of elasticity of the musculature may be approached with a resulting sharp rise in intraventricular pressure The consequent change in tension in the cusps of the auriculoventricular valves may be sufficiently great to produce an audible sound (Lewis and Dock) Most commonly this sound occurs at the time of auricular contraction (pre systolic gallop ta lubb dup ta lubb dup) but it may occur during the rapid filling phase of early diastole (protodiastolic gallop lubb dup ta lubb dup ta) Rarely when the rate is very rapid auricular contraction is superimposed on the rapid filling phase and the ventricular pressure change occurring with unusual abruptness a particularly loud sound is produced (summation gallop TA lubb dup TA lubb dup)

The recognition of gallop rhythm is of great practical importance because this phenomenon frequently is the earliest manifestation of impending congestive failure and even when failure is well advanced this disturbance in the heart sounds frequently is the only indication which can be elicited by examining the heart alone that a grave disturbance of function is present However the absence of gallop rhythm has no significance because this sign is lacking in a large proportion of patients with even advanced congestive failure

Manifestations of Failure of the Left Side of the Heart —When there is an impediment to the filling of the left ventricle either as the result of mitral stenosis or of the accumulation of so much residual blood consequent to dilatation that the left auricle does not empty readily the pressure rises in the pulmonary veins which are not protected by valves at their entrance into the atrium The consequent congestion of the lungs produces the characteristic symptoms and signs of left sided failure i e dyspnea cough rales in the lungs diminished vital capacity prolonged pulmonary circulation time accentuation of the pulmonary vascular shadows in the radiographic films and in certain patients cyanosis The mechanism whereby failure of the left side of the heart produces these several phenomena will be discussed later

Manifestations of Failure of the Right Side of the Heart — A rise in pressure in the pulmonary vascular bed whether occurring secondarily from congestion

disease of the heart occasionally occurs and although arrest of the disorder is not uncommon many of the patients pass progressively through a series of stages The proper recognition of this is important for upon it both treatment and prognosis depend The stages which are observed frequently are as follows

1 Potential heart disease The individual has neither symptoms nor signs of cardiac disease but is likely to develop it in the future Example an individual who has made an apparent complete recovery from a recent attack of rheumatic fever

2 Asymptomatic heart disease Here the patient has a definite objective manifestation such as slight enlargement or a diastolic murmur but has no subjective manifestations Example a patient with an early aortic valvular lesion and a normal exercise tolerance

3 Diminished cardiac reserve The patient with definite heart disease has no dyspnea at rest but suffers from it on the performance of an effort, which should not cause this symptom in a healthy person of similar age sex weight in proportion to height and habits as regards exercise Example the young woman with mitral stenosis who becomes out of breath on walking slowly up one flight of stairs

4 The stage of left sided heart failure In this phase of the disease the patient begins to have shortness of breath at rest Such dyspnea usually takes the form of orthopnea cardiac asthma, acute pulmonary edema, Cheyne Stokes respiration or some combination of these disturbances

5 The stage of right sided failure The patient who usually, but not invariably has suffered from failure of the left side of the heart now develops the additional phenomenon of venous distention enlargement of the liver edema etc

6 The stage of cardiac cachexia The subject who usually has had long standing failure of both sides of the heart may develop anorexia progressive loss of weight apathy weakness anemia and finally become remarkably emaciated With the modern understanding of the role and proper use of vitamins this pathetic state is seen less commonly than heretofore

Manifestations of Congestive Heart Failure

Having reviewed briefly the etiological factors and the several stages of heart disease, we may turn now to a consideration of those clinical phenomena, which appear in the more advanced phases of cardiac disease and which dominate the clinical syndrome of congestive heart failure It should be borne in mind that, while the diagnosis of heart disease is made by examining the heart the diagnosis of heart failure is made by examining the patient as a whole Nevertheless there are certain findings often encountered in the heart, which suggest that heart fail

duce the mean intrathoracic pressure and thereby to favor the inflow of blood to the chest which causes further pulmonary congestion in case the left side of the heart is more affected than the right as is the rule in patients subject to such seizures A vicious cycle may therefore ensue Whether the attack subsides as is usually the case or progresses to acute pulmonary edema as occasionally hap pens depends on the balance between these several alleviating and aggravating factors

Older patients with cardiac dyspnea frequently have seizures of *Cheyne Stokes respiration* which tend to occur especially at the onset of sleep As the patient dozes off apnea sets in lasting from a few seconds to nearly a minute When breathing starts it becomes progressively stronger the patient wakens and the increased sensitivity of the nervous system causes the respiratory movements to become still more violent due to the change from the sleeping to the waking state Eventually a peak is reached The diminuendo phase then sets in and the attack passes into the apneic phase

A common phenomenon is that which has been described as *evening dysp nea* Here even though the patient remains in bed throughout the day and in the same position he is relatively comfortable on first awakening in the morn ing and becomes progressively more dyspneic in the late afternoon and early evening

In the advanced stages of congestive failure patients may have *continuous dyspnea* with exacerbations of the several types described In a patient at rest the appearance of dyspnea lasting continuously for several days is an ominous prognostic sign

Finally one has to consider *dyspnea due to complications* such as pulmonary infarction hydrothorax complicating pneumonias etc

The understanding of the mechanisms concerned in cardiac dyspnea has been facilitated by the development within the past three decades of satisfactory meth ods of measuring the severity of this symptom in a rough fashion at least The pioneer studies of Peabody and his co workers on vital capacity[1 1] constituted the most important point of departure for the development of quantitative meth ods of measuring dyspnea It was suggested by them and later demonstrated by others[1] that the severity of dyspnea is in general in proportion to the closeness with which the actual volume of air breathed approaches the maximum volume which can be breathed per unit of time The actual volume can be measured easily by collecting the expired air The maximum possible volume per unit of time obviously is proportional to the maximum possible volume at a given breath i e to the vital capacity It was therefore shown by the author and his co workers that in the absence of special psychogenic disturbances and of condi tions which interfere with the free passage of air to and from the lungs the

brought about by left sided heart failure as usually is the case, or primarily from diseases of the pulmonary vessels or parenchyma, as is less frequently the case results in increased work for the right ventricle A rise in pulmonary arterial pressure of as little as 10 to 15 mm of mercury constitutes an important degree of pulmonary hypertension because the pressure in this artery is normally only about one fourth that in the aorta, and thereby inflicts a heavy load on the right ventricle which ordinarily is only about one third as thick as the left Since, as Starling showed the physiological response of the heart to augmented work is increase in the length of muscle fibers the right ventricle dilates and eventually the additional residual blood offers impediment to diastolic filling The subsequent rise in venous pressure is generally believed to be primarily responsible for all of the major phenomena of right sided heart failure including venous distention enlargement of the liver cyanosis if not due to arterial anoxia albuminuria edema and prolongation of the "arm to lung" circulation time

Having summarized the chief causes stages and manifestations of congestive heart failure, we may now properly proceed to the consideration of the mechanisms of disordered function which produce the clinical picture

Mechanism of the Clinical Manifestations of Failure of the Left Side of the Heart

Dyspnea — Dyspnea may be defined as the consciousness of distress in breathing At first it appears only on exertion the degree of exercise required to induce it becoming progressively less Later shortness of wind begins to appear in the resting state usually first taking the form of *orthopnea* in which the patient needs to be propped up by several pillows in order to be comfortable Many patients have attacks of "*cardiac asthma*" i e seizures in which they waken usually from a sound sleep with severe attacks of shortness of breath go to the window for a few minutes, assume the upright position and perhaps expectorate a small amount of sputum Usually the attack subsides but occasionally it becomes progressively severe and passes on into acute pulmonary edema, which sometimes is fatal This difference of behavior during different attacks probably is to be explained by a balance of various factors The upright posture tends to drain blood out of the lungs and into the abdomen and lower extremities This change as indicated later on tends to reduce dyspnea Likewise the patient when he awakens often gets rid of sputum which was causing irritation and was affecting the breathing or attends to various other functions such as urination belching the expulsion of flatus and adjustment of the bedclothes all of which may be concerned in the induction of the attack On the other hand the dyspnea itself, mainly a result of pulmonary congestion as indicated later on tends to re

coexists one cannot account for cardiac dyspnea on a purely chemical basis Evidently other factors must be involved

Extensive studies have been made of the several types of cardiac dyspnea in order to determine the various mechanisms which can be held accountable for the increased minute volume of breathing These have been published in detail elsewhere[1] and need only be summarized here

It has been shown that in the case of *dyspnea on exertion* the following factors are concerned

1 During severe exertion well marked changes in hydrogen ion concentration of arterial and venous blood occur, and these are sufficient to explain the major part of the respiratory stimulation However in the case of mild exertion equivalent to walking at a slow rate which is sufficient to induce dyspnea in patients with congestive failure there is not only a lack of a shift in the blood toward the acid side but the opposite condition actually may occur in the sense that the blood becomes slightly more alkaline the carbon dioxide tension declines and the arterial oxygen increases

2 The most important factor in the production of respiratory stimulation on mild exertion is of reflex origin and is due to the effect of afferent impulses arising in the moving muscles and joints[13] These affect the respiratory center and stimulate the breathing Another but somewhat less important factor is of interest because it probably explains the observation that for a given exercise cardiac patients exhibit greater increase in breathing than normal subjects even though the amount of muscular movement is the same and therefore the stimulation of afferent impulses from the moving part should be the same It has been shown that just as a rise in venous pressure causes an increase in pulse rate through the reflex mechanism first described by Bainbridge[17] so the same change results in an increase of breathing Thus a rise in venous pressure induced in various ways in the great veins close to the heart and in the right auricle causes respiratory stimulation such an effect being absent if the vagus nerves have been cut previously[14] However it should be emphasized that changes produced in this manner are not great and that the increased respiratory minute volume occurring on mild exertion is mainly to be attributed to the reflex respiratory stimulation from the moving parts the greater rise in venous pressure which occurs in cardiac patients compared to the normal subject performing the same exertion being a less important factor

The *mechanism of orthopnea* is fairly simple Even at rest the factors of diminished vital capacity and pulmonary congestion result either in actual dyspnea or in the tendency toward it When the person lies down the vital capacity decreases and this decline usually is greater in the cardiac patient than in the normal subject as Christie and Beams[18] first showed Such a further decline in

expression $\frac{\text{ventilation}}{\text{vital capacity}}$ constituted a reasonably accurate quantitative guide to the severity of dyspnea. The problems of the mechanism of dyspnea may, therefore, be subdivided into two questions: (1) why is the vital capacity decreased? and (2) why is the volume of air breathed increased?

As regards the first of these questions there would seem to be no doubt. Observations at the autopsy table indicate beyond question that the chief cause, aside from such complicating factors as hydrothorax, pneumonia, infarction and co-existing diseases such as emphysema, of the decrease in vital capacity is pulmonary congestion. It follows, therefore, that for any given degree of respiratory effort the amount of air entering the lungs will be reduced. Hence, the decrease in vital capacity consequent to pulmonary congestion sets up a state in which for any given amount of air breathed per unit of time the degree of respiratory effort, which is proportional to the actual dyspnea or the tendency toward dyspnea, will be augmented.

However, this is not the whole story. The patient with left-sided heart failure and consequent pulmonary congestion suffers not only from diminished vital capacity but in most instances has an actual increase in the volume of air breathed per minute. The mechanism of this increase is of great importance in understanding the pathogenesis of cardiac dyspnea. It was believed formerly that the interference with proper aeration of the lungs led to a condition of deficient gaseous exchange from the blood. However, analyses conducted on arterial blood in cardiac patients under various conditions[13, 14] have shown that this assumption ordinarily is valid only when there is either pulmonary edema, emphysema, infarction of the lungs, pneumonia or some other complicating factor. In the majority of patients with congestive heart failure the arterial blood contains a normal or somewhat increased amount of oxygen, and the carbon dioxide tension is normal or slightly diminished. Such alterations can only be the effects, and not the causes, of the respiratory stimulation. Hence we have to look elsewhere for the explanation of the increase in pulmonary ventilation in patients suffering from cardiac dyspnea.

Another suggestion which has been offered is that because of congestive heart failure the flow of blood through the *brain* proceeds at a diminished volume per unit of time, and that this interferes with gaseous exchange and stimulates the respiratory center. This assumption likewise has been shown to be incorrect because analyses of blood from the internal jugular vein, as obtained from non-dyspneic and dyspneic cardiacs, when compared to similar analyses made on the blood obtained from the same vein in normal persons, offer no support for the assumption[13, 14]. It is therefore clear that, except in the presence of such complications as have been mentioned or when acute heart failure (forward failure)

from a loss of carbon dioxide This probably accounts for the hyperpneic portion of the cycle After a time the hemoglobin is completely oxygenated in the arterial blood and from this point on the effect of the loss of carbon dioxide predominates and the blood tends to become somewhat more alkaline resulting in the diminuendo phase Eventually because of loss of carbon dioxide apnea ensues and when this has proceeded sufficiently long for the oxygen supply in the lungs to be seriously depleted there is a rapid shift in the degree of oxygenation of the arterial blood which begins to contain progressively larger quantities of reduced hemoglobin This results in the further increase in alkalinity with prolongation of the apneic phase Eventually however, the increase in CO tension due to the cessation of breathing tends to cause respiration to begin and the cycle repeats itself It has not yet been shown that such a mechanism is important in all cases but undoubtedly it is prominent in many cases of Cheyne Stokes breathing

The mechanism of *continuous dyspnea* is like that of orthopnea except that here the degree of pulmonary congestion is so great that even when the patient is at rest and sitting upright there is enough decline in vital capacity and increase in the volume of air breathed to produce the labored breathing which is interpreted in the patient s sensorium as dyspnea Obviously the discomfort is aggravated by assumption of the recumbent position by the increased metabolic activities of the day and is complicated frequently at night by paroxysmal seizures of either the Cheyne Stokes or cardiac asthma type Thus the patient with continuous dyspnea usually exhibits most if not all of the other forms of cardiac dyspnea

The mechanisms which have been described are those which were worked out some fifteen years ago and which are accepted generally In recent years certain work has been published which would tend to indicate that the factors mentioned are of less importance than is generally believed Thus Altschule Iglauer and Zamcheck have pointed out that dyspnea and orthopnea frequently are present in patients with obstruction of the vena cava They believe that stasis of the blood in the brain may be the chief factor This concept is difficult to reconcile with the observation that compression of the neck in normal subjects does not produce dyspnea * Furthermore Altschule and his associates did not make analyses of the blood from the jugular veins and therefore did not present direct evidence in support of the contention of cerebral stasis Secondly, it should be noted that their patients with superior caval obstruction but without heart failure also had a decline in vital capacity and that in two of the three subjects improvement in dyspnea was associated with a rise in vital capacity

It has been shown * that increase in cerebrospinal fluid pressure tends to cause dyspnea and it is possible that this mechanism may be concerned in the production of orthopnea in patients with caval obstruction However the

vital capacity consequent to the effect of gravity and probably due to the elevation of the diaphragm plus an increased degree of pulmonary congestion, results in a further diminution in the maximal possible ventilation Since both atelectasis and congestion[1] cause reflex stimulation of breathing through the Hering Brauer reflex the recumbent posture tends to increase the actual ventilation also and thereby causes a disproportionate increase in the tendency toward dyspnea *

The mechanism of *evening dyspnea* is in all probability the same as that of orthopnea but in this case the increased activity of the day as compared to the night tends to cause some increase in pulmonary congestion as the day wears on and hence produces both decline in vital capacity and increase in volume of air breathed

Cardiac asthma is a complex phenomenon The fundamental factor which loads the gun is pulmonary congestion [6] However, the mechanisms which pull the trigger and set off the attack are not entirely understood According to studies made by the author and his colleagues there are numerous such mechanisms the chief among them being the more horizontal posture during sleep the respiratory stimulation resulting from apprehension associated with nightmares and unpleasant dreams excessive warmth due to the bedclothes and the reflex effects of distention of the gastrointestinal organs or of the bladder Another important trigger factor is the shift in water from the tissues into the blood stream which occurs during the earlier hours of sleep as postulated by Brunn [7] and Gollwitzer Meier and recently demonstrated by Perera and Berliner It is probable that there are other trigger mechanisms which are not understood as yet All such initiating factors tend to stimulate breathing to increase venous inflow and hence to augment the degree of pulmonary congestion which Weiss and Robb [4] showed to be the outstanding feature of the attack

Cheyne Stokes respiration is also a complicated phenomenon and its mechanism is not completely understood Possibly there is some distortion in the normal regulatory relationships between the carotid sinus the carotid body and the respiratory center However this has not been proven for patients with cardiac disease In any case it would seem that one important factor responsible for the diminuendo crescendo and apneic phases is to be found in the alterations in pH induced in the blood by rapid changes in the degree of oxygenation of the hemoglobin Thus at the end of the apneic phase when the breathing begins there is a rather sudden change in the arterial blood from a state of unsaturation to saturation Since oxyhemoglobin is more acid than reduced hemoglobin there is during the crescendo phase a rapid increase in hydrogen ion concentration from this cause which overbalances the tendency in the opposite direction, resulting

* Certain recent observations tending to explain orthopnea on a different basis will be discussed later

produce edema in the alveolar spaces) As already has been pointed out acute pulmonary edema occurs when there is sudden pulmonary congestion of severe degree attended by rapid transudation of fluid into the alveolar spaces

The *prolonged circulation time through the lungs* often has been misinterpreted as indicating that the actual flow of blood through the lungs per unit of time is decreased This is not necessarily correct because the cardiac output per minute in many patients with congestive failure is either normal or slightly subnormal The chief factor responsible for prolonged circulation time is the increase in size of the pulmonary vascular bed as the result of congestion Similarly the prominent vascular shadows in the x ray can be ascribed to dilatation of the vessels because of engorgement

Mechanism of the Clinical Manifestations of Failure of the Right Side of the Heart

The pathogenesis of most of the phenomena of right sided failure would seem to be clear That congestion of the kidneys produces albuminuria and minimal slight hematuria can be shown experimentally by partial obstruction of the renal vein Similarly cyanosis can be produced by increased venous pressure as anyone can demonstrate readily by holding his hand below the level of the heart and observing the change in color of the finger nails A large tender liver apparently is the result of congestion because of increased venous pressure the degree of tenderness depending on how much the capsule is being stretched in relation to previous stretching Thus a slightly enlarged liver which has never been engorged before may be painful whereas a very large liver which is somewhat smaller than before usually is painless because the peritoneal coat of the liver having once been stretched markedly is no longer stretched as much as before and the tension on it has been relieved

Mechanism of Edema Formation — The chief discussion in regard to heart failure during recent years has been concerned with the mechanism of edema formation The view which has the predominant weight of evidence behind it is that which follows from the original back pressure concept as so clearly elaborated more than a hundred years ago by James Hope [1] and which attributed the edema to increased capillary pressure secondary to increase in venous pressure Since it was shown by Starling[3] nearly fifty years ago that the chief factors which govern the passage of fluid through capillary membranes are the mechanical pressure in the capillaries tending to force water out and the colloid osmotic pressure of the plasma proteins tending to draw water in it has been assumed logically that the increase in venous pressure and hence in lymphatic and capillary pressure in congestive heart failure is the primary and fundamental factor in caus

available evidence suggests that in patients with congestive failure the pulmonary engorgement is the factor of chief importance

Another recent report by Altschule and his colleagues [7] is of interest They studied patients with orthopnea and, having found no consistent alteration in the relationship of residual air to total capacity in the recumbent as compared to the sitting position concluded that the degree of pulmonary congestion was not increased by recumbency Such a conclusion is open to two serious objections In the first place the method used for measuring lung volume and its subdivisions depends on obtaining homogeneous gas mixtures throughout the lungs Such homogeneity is attained with difficulty in the recumbent position in normal subjects and probably cannot be achieved at all in this position in many patients with cardiac disease Secondly even if one assumes validity of the method utilized the data do not offer strong support for the conclusion drawn When a normal subject changes from the sitting to the supine position, there is a marked decrease in the functional residual air due to the ascent of the diaphragm In the normal subjects studied by McMichael and McGibbon [9] this change averaged 780 c c or approximately 13 per cent of the total lung volume On the other hand in the orthopneic cardiac patients studied by Altschule Zamcheck and Iglauer [7] the average decrease in the functional residual air in the recumbent position was 149 c c or 6 3 per cent of the total lung volume In other words the normal tendency toward the development of relative atelectasis in the recumbent position is markedly diminished in patients with congestive failure It is difficult to see what mechanism other than increased rigidity of the lungs resulting from augmented pulmonary congestion in the recumbent posture can account for this difference in the behavior of the orthopneic patient from the normal subject Apparently the increased pulmonary rigidity (*Lungenstarre*) is important in reducing the vital capacity while the additional blood in the lungs (*Lungenschwellung*) tends to stimulate the breathing both factors favoring the production of dyspnea

In the light of these considerations it would seem justifiable to conclude that there is as yet no valid evidence *against* the concept that increased degree of pulmonary congestion in the recumbent posture is a factor of major importance in the production of orthopnea in patients with congestive heart failure

The mechanism of the other signs of failure of the left side of the heart would seem to be fairly obvious Presumably the *cough* and the *wheezing*, which occasionally occur are dependent on congestion and edema of the bronchi The appearance of *rales at the lung bases* simply means that pulmonary congestion has proceeded far enough to produce edema (*It is a common error to assume that the absence of rales means that the lungs are not congested* Actually the absence of rales means only that the congestion has not proceeded far enough to

tion of cardiac edema rather than to the apparently sounder conclusion that the sodium balance determines not whether edema will form but the degree to which it will form The fact that by restriction of sodium and by the use of procedures such as liberal amounts of water and acidifying measures which tend to increase sodium excretion one can get rid of edema does not mean that sodium retention is the primary cause of cardiac edema Such conclusion is almost as illogical as the conclusion that, because digitalis helps congestive failure the lack of digitalis is the cause of it

The evidence on which the sodium retention theory as the primary mechanism of cardiac edema formation is based is as follows

(1) Restriction of sodium and measures which tend to increase its excretion, are very efficacious in overcoming edema The lack of validity of this point has just been mentioned

(2) The administration of sodium chloride aggravates the tendency to edema formation However, it is well known that the administration of large amounts of sodium to patients with diabetes tends to cause edema formation Is one to assume that in such individuals who have no evidence of heart failure or often no evidence of heart disease the edema is of cardiac origin? Likewise one may even produce edema although usually of minimal degree in perfectly normal subjects by the ingestion of large amounts of salt Is one to assume that healthy young men who gain a few pounds of weight when ingesting twenty or more grams of sodium chloride per day have heart failure? It seems clear that the mistake has been made of drawing conclusions about one form of edema cardiac by studying another form of edema that due to sodium retention

(3) It has been found that in patients with congestive heart failure there may be even in the presence of a normal or only slightly diminished cardiac output, a well marked decrease in renal blood flow This has led to the concept that the decrease in renal blood flow alters the kidney in such a way that salt is retained and that such retention is the primary cause of cardiac edema If diminished renal blood flow is responsible for cardiac edema one would expect edema to occur in all patients with comparable diminution in renal blood flow as the result of glomerulonephritis or of nephrosclerosis The studies of Goldring Chasis Ranges and Smith[36] as well as those of Corcoran and Page[37] do not substantiate this assumption Likewise if diminished renal blood flow can cause sodium retention and consequent edema one would expect that any dog subjected to the Goldblatt procedure with the arterial clamp tight enough to materially reduce the renal circulation would develop well marked edema Such is not the case

(4) It has been shown that the administration of large volumes of salt to patients with impending congestive failure may lead to edema as shown by increase in weight, prior to rise in venous pressure[38] The secondary rise in the

ing edema formation According to this conception edema in heart disease is not unlike that which develops in the hand when a tourniquet is placed around the arm and is left on the arm at a pressure of 30 mm of mercury for a period of time

The concept that increased venous and capillary pressure is the dominant factor in the causation of cardiac edema does not mean that other factors do not enter the picture. One of these is the level of the plasma protein which although often normal is not infrequently somewhat reduced in patients with long standing heart disease Another important factor, to which relatively little attention has been paid is the lymph flow The ability of the tissues to resist stretching i e the mechanical pressure likewise is important and under exceptional conditions such as when inflammation coexists an increase in the colloid osmotic pressure of the tissue fluids may occur also Finally there is the important factor of intake of salt and of water concerning which so much has been written in recent years Some observers have gone so far as to assume that retention of sodium is the initial and primary factor in the edema of congestive heart failure It is believed that the discussion to follow will demonstrate that such is not the case, and that we are still justified in believing that the primary condition which determines whether or not edema will occur is the venous pressure but that the other factors mentioned and more particularly the intake and excretion of sodium are of great importance in determining how much edema occurs

In the earlier part of the present century a number of writers particularly in France emphasized the importance of chloride retention in edema due to cardiac and other diseases With the demonstration that chloride in the form of the ammonium or potassium salts actually may have a diuretic effect this concept was shown to be unsound and many investigators including the writer went to the opposite extreme and assumed that it was the water rather than the salt intake which was of dominant importance The unsoundness of this concept was demonstrated by a number of workers including Schroeder[33] who showed clearly in well controlled studies that sodium rather than water intake was of importance in relation to the edema of cardiac failure Indeed it has been shown in recent years by the important clinical observations of Schemm[34 35] that water tends to be a diuretic provided patients are given a diet which is extremely low in sodium and provided acidifying measures acid ash diet or administration of ammonium salts or of hydrochloric acid are employed to increase the excretion of sodium

The soundness of the clinical observations of Schroeder and of Schemm is in general beyond question These observations and somewhat similar ones conducted by others have led in recent years to the renewal of the discussion concerning the mechanism of edema formation in patients with congestive heart failure The demonstration of the importance of intake and excretion of sodium has led some to the conclusion that these are the primary factors in the produc

citation of isolated case reports [1] and also observations in which experimentally produced injury to the right ventricle in animals has not resulted in a corresponding increase in venous pressure[4] However congestive failure is notoriously difficult to produce in normal animals because of the large factor of reserve in the heart The observation that right ventricular injury did not in a few dogs lead to increased venous pressure does not indicate that diffuse strain on the right ventricle or even localized injury if sufficiently wide spread and of long enough duration would not have such a consequence The evidence derived from such negative experiments and from isolated case reports is not convincing when balanced against the almost overwhelming evidence derived from clinical observation and from measurements of vital capacity circulation time venous pressure and other circulatory functions These studies indicate that independent failure of one side of the heart not only may occur but frequently does occur

This brief summary of some of the recent work most of it excellent in itself which has been interpreted as throwing serious doubt on the validity of such important hypotheses as Starling s law and James Hope s back pressure idea of heart failure would seem to lead to the conclusion that these fundamental concepts still have not been seriously challenged by either experimental or clinical observations

Such a conclusion is not only of academic interest but of practical therapeutic importance If we should return to the now discarded and discredited forward failure theory, which holds that the manifestations of such major symptoms of congestive heart failure as dyspnea and edema are due to diminished blood supply to the tissues then the separation between peripheral circulatory failure forward failure of the circulation and backward failure congestive heart failure would vanish and there might once again be a tendency to treat all such cases alike Patients suffering from hemorrhage Addisonian crises surgical shock etc might again be given digitalis indiscriminately with results which would not only be useless but harmful In the final analysis sound practice ultimately will depend on sound theory

The purpose of the foregoing discussion has been to point out that there is a clear distinction between backward failure of the circulation congestive heart failure and forward failure whether the latter be as is usually the case of peripheral origin or as is less frequently the case of cardiac origin The two types of circulatory failure may occur together but usually do not Until more thorough and more convincing evidence is forthcoming probably we shall be safe in assuming that the concepts advanced by James Hope more than a century ago and for that matter hinted at by Harvey more than three centuries ago are still correct and that the symptoms and signs of congestive heart failure are to be predominantly ascribed to engorgement either in the pulmonary vascular bed as result

latter function has been thought to be the result of the increase in extracellular fluid volume Against this concept of the relationship between cardiac edema and venous pressure the following evidence may be cited

(a) The type of edema studied is that due to salt retention, and the fact that it was produced in patients with cardiac disease does not mean that the mechanism of such artificially induced edema is necessarily the same as that occurring spontaneously as the result of heart failure

(b) If the presence of edema per se tends to cause rise in venous pressure, one would expect to find elevation of this function in patients with dropsy due to hypoproteinemia Such is not the case

(c) Reichsman and Grant have shown that healthy young men taking 20 gm of sodium chloride per day and remaining actively at work develop a rise in venous pressure before displaying edema as indicated by gain in weight Their work would suggest that the increase in venous pressure resulting from excessive sodium intake is due to increase in blood volume and not to edema

(d) Reichsman and Grant have found also that in certain patients with auricular fibrillation withdrawal of digitalis the sodium intake being left constant at a normal level results in rise in venous pressure prior to the development edema

The observations cited would seem to indicate that the concept of sodium retention as the primary cause of cardiac edema is not supported by the available evidence

Another apparently mistaken conception concerning right sided heart failure has been advanced recently, namely that all patients with acute nephritis display this phenomenon and that the edema of acute nephritis is due to right sided heart failure This conclusion is based on the observation that patients with acute nephritis show an elevation of venous pressure[4] However, Reichsman and Grant[3] have shown recently that normal young men by taking o grams of sodium chloride per day while maintaining normal activity may develop increase in venous pressure before displaying significant gain in weight We cannot assume that such healthy subjects who are able to work sixteen hours a day in the presence of such moderate elevation of venous pressure and who have no indication whatever of heart disease have suddenly developed heart failure

We are, similarly not justified in assuming that all patients with acute nephritis have heart failure Some of them do develop congestive failure but the rise in venous pressure which may result from sodium retention is not per se adequate grounds for assuming that congestive failure is present

Certain recently published reports which have tended to question the generally accepted concept of independent failure of one side of the heart include

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19 CALHOUN J A CULLEN G E HARRISON T R WILKINS W E and TIMS M M Studies in congestive he rt failure XIV Orthopnea its rel tion to ventilation vital capacity o ygen aturation and acid base condition of arteri l and jugular blood Jour Cl n Invest 1931 X 833

o HARRISON T R CALHOUN J A and HARRISON W G JR Congestive heart failure XXI Observations concerning the mechanism of cardiac asthma Arch Int Med 1934 LIII 911

1 BRUNN Fr Über Asthma cardiale Zentralbl f inner Med 19 8 XLIX 8/3

2 GOLLWITZER-MEIER K Anfallsweise At mnot der H rzkranken und Hypertoniker Klin Wochenschr 1931 X 341

23 PERERA G A and BERLINER R H The relation of postural hemodilution to paroxysmal dyspnea Jour Clin Invest 1934 XXII 5

4 WEISS S and ROBB G P Cardiac asthma (p roxysmal cardiac dyspnea) and syndrome of left ventricul r failure Jour Am Med Assoc 1933 C 1841

5 ALTSCHULE M D ZAMCHECK N and IGLAUER A Lung volume and its subdivisions in upright and recumbent position in patients with conge tive failure Jour Clin Inve t 1943 XXII 805

6 HARRISON W G JR The ci ternal pres ure in congestive heart failure and its bearing on orthopnea Jour Clin Invest 1933 XII 10 5

27 ALTSCHULE M D ZAMCHECK N and IGLAUER A The lung volume and its subdivisions in the upright and recumbent po itions in patients with congestive failure Pulmonary factors in the genesis of orthopnea Jour Clin Invest 1943 XXII 805

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33 FUTCHER P H and SCHROEDER H A Studies on congestive heart failure impaired renal excretion of sodium chloride Am Jour Med Sci 1942 CCIV 52

of left sided heart failure, producing dyspnea as the outstanding manifestations or in the systemic vascular bed as the result of right sided heart failure, producing edema as the most striking clinical phenomenon

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10 PEABODY F W Clinical studies on the respiration III A mechanical factor in the production of dyspnea in patients with cardiac disease Arch Int Med 1917 XX 433
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CHAPTER XIII-E

SHOCK SYNDROME IN INTERNAL MEDICINE

By EUGENE A STEAD JR

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Definition

The term shock is commonly used to describe a clinical picture characterized by prostration and by a sharp fall in arterial pressure or by the signs and symptoms of a decrease in cardiac output Numerous descriptive adjectives have been added in an effort to indicate the etiology of the prostration and circulatory failure Thus the terms surgical traumatic primary secondary medical hemorrhagic and cardiac shock have been used

Various physiologists and physicians have attempted to restrict the use of the terms shock secondary shock and surgical shock to circulatory insufficiency caused by a failure of the venous return to the heart This usage has not gained general acceptance because clinical experience has demonstrated that the physi

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December 1 1945

factor in the circulatory failure produced by trauma and burns but that infection tissue necrosis and reflex disturbances play an important role in many patients In the conditions so far studied in man infection and tissue necrosis produce their effects by interfering with cell metabolism throughout the body rather than by specifically injuring the capillaries throughout the body and causing them to leak protein[11, 12] Reflex arteriolar dilatation from painful, visceral or psychic stimuli also play an important role in many instances

Clinical Picture of Shock

The patient in shock usually is pale with moist skin and cold extremities Epigastric distress nausea and vomiting are common He may be listless and apathetic restless and apprehensive confused and manic The systolic arterial pressure is low, the pulse pressure narrow the heart rate is rapid and the radial pulse of poor volume The body temperature is subnormal the veins of the extremities and neck are collapsed and fill slowly when their outflow is obstructed The blood removed from the antecubital vein is dark in color because of the slow blood flow

There are many exceptions to the classical picture A marked fall in arterial pressure may occur with warm skin and with veins which fill rapidly when the venous outflow is obstructed The skin may be red rather than pale Mental symptoms may be absent In certain patients the heart rate is slow in others the arterial pressure is well maintained in still others the venous pressure may be raised When infection is present the rectal temperature may be elevated even though the skin is cold

In each instance the patient appears ill and there are signs of circulatory insufficiency or a fall in arterial pressure In practice the term shock is applied to all types of general circulatory insufficiency in which the manifestations of congestive heart failure are not obvious

Pathological Physiology of Shock

The corollary of the concept that shock describes a clinical syndrome rather than a condition produced by a specific disturbance in function is that shock may be caused by failure of one of several portions of the circulation The following disturbances in function may produce the clinical picture of shock (1) inability of the heart to pump the needed blood because of weakness of the heart itself (2) failure of the heart to fill properly because of pericardial tamponade (3) obstruction of the main arterial pathways as in a massive pulmonary embolus (4) failure of the heart to pump the needed blood not because of weakness

cian many times cannot determine at once the physiological basis of the circulatory failure He desires to describe in a word a clinical picture of severe prostration accompanied by the peripheral signs and symptoms of circulatory insufficiency without committing himself to the cause of the circulatory failure By common use the word shock has become entrenched in this sense, and it does not seem wise or possible to attempt to change its meaning Various syndromes characterized by a sudden depression of cellular function not accompanied by circulatory insufficiency also are called shock Insulin shock is a good example of this group They will not be included in this discussion

Theories of the Etiology of Shock

For a long time it was not realized that the clinical picture called shock was produced by a variety of mechanisms Many theories as to the cause of shock were advanced but in the light of present day knowledge no one of them is capable of explaining the varieties of circulatory failure classified as shock

Meltzer[1] advanced the theory that shock was caused by reflex inhibition of the various functions of the body Mitchell Morehouse and Keen and Fisher[3] believed that reflex vasomotor paralysis caused shock Crile[4] assumed that the fall in blood pressure was the result of exhaustion of the vasomotor system The suggestion that shock could be accounted for by the plugging of vessels with fat was made by Bissell[5] and Porter[6] Both adrenal hyperactivity and adrenal exhaustion have been advanced as the cause of shock but observations on patients have lent no support to either hypothesis Cannon[7] concluded "The theory of secondary shock which has the strongest support both in clinical observations and in laboratory experiments is that of a toxic factor operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the tissues" Moon[8] has vigorously supported the toxic theory of shock

Blalock and his associates[9] have demonstrated that in crushing injuries the local loss of fluid into injured tissues either plasma or whole blood is sufficient to produce a small blood volume and that it is not necessary to postulate a toxic factor which causes a generalized increase in capillary permeability in order to account for the small blood volume and circulatory failure

Aub and his associates[10] have agreed with Blalock as to the importance of local fluid loss in traumatic shock but in dogs they have found that the injured muscle frequently is infected with clostridia They believe that infection is the toxic factor in traumatic shock in dogs

It is now generally accepted that in man the loss of fluid from the blood stream by bleeding or by loss of plasma into injured areas is a very important

quate venous return to the heart In other words shock occurs because of blocked inflow to the heart If the tamponade is reduced by aspiration or operation the circulation improves and the evidences of shock disappear

Shock Caused by Massive Pulmonary Embolus — Shock may be produced by blocking the flow of blood through the major arteries Such a situation is seen in patients with massive pulmonary emboli and in patients in whom the pulmonary capillaries are plugged with neoplastic tissue Small pulmonary emboli may be associated also with circulatory failure but it is very likely that the mechanism in these patients is more complex Tissue necrosis resulting in changes in cell metabolism and reflexes from the involved lung probably play an important part in producing the shock syndrome

Shock Produced by Loss of Blood Plasma or Fluid — Patients with massive hemorrhage develop the clinical picture of shock As the blood volume decreases the venous return to the heart becomes inadequate and the output of the heart decreases The heart cannot pump any more blood than it receives That this circulatory failure is the result of a decrease in blood volume can be easily proven Transfusions of blood or plasma raise the atrial pressure increase the filling of the heart and restore the circulation to normal

Hemorrhage may be of many types It may be external or it may be internal into body cavities or into the tissues themselves It may be selective in type When the capillaries are injured but are not completely broken asunder as in chemical peritonitis following a ruptured ulcer in burns or in certain types of crushing injuries plasma may leak through the injured vessels although the capillary walls still hold the red cells within the vascular bed This type of selective hemorrhage plasma loss can result in a small blood volume and circulatory failure The cardiac output decreases because of decrease in venous return to the heart That the circulatory failure is produced by the small blood volume is demonstrated again by an immediate response to plasma or whole blood Increased permeability of the capillaries which allows plasma to leave the blood stream occurs at the site of injury or infection Capillaries in areas of the body not directly involved by the injury do not leak protein abnormally[11]

In continued vomiting severe diarrhea or Addison s disease sufficient electrolytes and water may be lost from the body to produce circulatory failure on the basis of a small blood volume The administration of physiological salt solution will increase the blood volume and improve the circulation

In patients with dehydration external or internal hemorrhage or plasma loss into the body cavities or tissues the decrease in blood volume may be marked before there are any clinical signs of circulatory insufficiency This is not unexpected because experience with blood donors has demonstrated that the circulatory system has the ability to compensate for a moderate decrease in blood

of the heart but because the venous inflow to the heart has failed (5) wide spread failure of cell metabolism, (6) loss of vasoconstrictor tone

Shock Caused by Failure of the Heart — Patients with very rapid heart rates from paroxysmal auricular tachycardia, ventricular tachycardia or auricular flutter may demonstrate all of the classical signs and symptoms of shock In deed on first seeing the patient it may not be apparent at once that poor heart action is the basis for the circulatory failure The heart is not functioning effi ciently as a pump because diastole is too short to allow adequate filling of the heart The clinician says that the patient has shock because of the appearance of the patient the physiologist says that the patient has circulatory insufficiency because of inadequate cardiac output Slowing of the cardiac rate improves the patient and cures the sh ck

Patients with recent massive myocardial infarctions involving the left ven tricle may present the classical manifestations of shock[13] Some authors have proposed other terms such as cardiac collapse '[14] for this condition while others use the simple descriptive term shock The venous return to the heart is normal but the heart is weakened so that it cannot maintain a normal output of blood The left ventricle usually is injured to a greater extent than the right The right ventricle floods the lungs with blood, which the left ventricle cannot move on and the patient may show marked pulmonary congestion in addition to the signs and symptoms of shock Increasing the venous pressure by transfusions or decreasing it by venesection has little effect on the patient s condition, because the primary disorder is in the heart itself[1]

In the terminal stages of cardiac failure no matter what its cause one may see the evidence of shock superimposed upon the manifestations of congestive heart failure Here just as in the case of myocardial infarction the heart itself is at fault and the symptoms result from diminished cardiac output in the same fashion A less common type of circulatory disturbance is that seen as the result of certain poisonings such as acute phosphorus poisoning where there appears to be a severe degree of myocardial damage as a result of the direct action of the chemical[15]

Shock Caused by Pericardial Tamponade — Acute pericardial tamponade from a stab wound of the heart or from a rapidly forming pericardial effu ion causes the typical picture of shock The pallor sweating nausea and restlessness with the low arterial pressure weak or absent radial pulse and the cold extremi ties present a striking picture of acute circulatory failure On close observation the venous pressure is found to be increased but because the veins are not dilated, as is frequently the case in congestive failure the high venous pressure may be overlooked The radial pulse is paradoxical The circulatory impair ment is the result of elevated intrapericardial pressure which prevents an ade

quate venous return to the heart In other words shock occurs because of blocked inflow to the heart If the tamponade is reduced by aspiration or operation the circulation improves and the evidences of shock disappear

Shock Caused by Massive Pulmonary Embolus — Shock may be produced by blocking the flow of blood through the major arteries Such a situation is seen in patients with massive pulmonary emboli and in patients in whom the pulmonary capillaries are plugged with neoplastic tissue Small pulmonary emboli may be associated also with circulatory failure but it is very likely that the mechanism in these patients is more complex Tissue necrosis resulting in changes in cell metabolism and reflexes from the involved lung probably play an important part in producing the shock syndrome

Shock Produced by Loss of Blood Plasma or Fluid — Patients with massive hemorrhage develop the clinical picture of shock[9] As the blood volume decreases the venous return to the heart becomes inadequate and the output of the heart decreases The heart cannot pump any more blood than it receives That this circulatory failure is the result of a decrease in blood volume can be easily proven Transfusions of blood or plasma raise the atrial pressure increase the filling of the heart and restore the circulation to normal

Hemorrhage may be of many types It may be external or it may be internal into body cavities or into the tissues themselves It may be selective in type When the capillaries are injured but are not completely broken asunder as in chemical peritonitis following a ruptured ulcer in burns or in certain types of crushing injuries, plasma may leak through the injured vessels although the capillary walls still hold the red cells within the vascular bed This type of selective hemorrhage plasma loss can result in a small blood volume and circulatory failure The cardiac output decreases because of decrease in venous return to the heart That the circulatory failure is produced by the small blood volume is demonstrated again by an immediate response to plasma or whole blood Increased permeability of the capillaries which allows plasma to leave the blood stream occurs at the site of injury or infection Capillaries in areas of the body not directly involved by the injury do not leak protein abnormally[11 1]

In continued vomiting severe diarrhea or Addison s disease sufficient electrolytes and water may be lost from the body to produce circulatory failure on the basis of a small blood volume The administration of physiological salt solution will increase the blood volume and improve the circulation

In patients with dehydration external or internal hemorrhage or plasma loss into the body cavities or tissues the decrease in blood volume may be marked before there are any clinical signs of circulatory insufficiency This is not unexpected because experience with blood donors has demonstrated that the circulatory system has the ability to compensate for a moderate decrease in blood

volume If a normal man weighing 180 lbs is lying in the horizontal position at least 1 000 c c of blood can be removed rapidly without producing any symptoms There will be no change in blood pressure and only a slight rise in pulse rate unless the patient faints from the emotional reaction associated with the blood letting If one continues to remove blood the circulation will fail

Various authors have attempted to distinguish between the mechanism of the circulatory failure caused by external hemorrhage and that present in other forms of circulatory failure caused by a small blood volume [11] This distinction seems unwarranted to the physician actually caring for patients The similar response to an increase in the blood volume in the patient with simple hemorrhage and in the patient with more selective loss of fluid from the blood stream such as seen in dehydration or plasma loss convinces him that both types of circulatory failure result from a small blood volume It is true of course, that the blood tends to be diluted after hemorrhage and concentrated after a burn but these differences are the result of the type of fluid lost from the blood stream and are not indicative of a fundamental difference in the mechanism of circulatory failure In patients with burns or extensive trauma the circulatory failure produced by a small blood volume may be accentuated by the effect on cell metabolism from absorption of the products of infection or tissue necrosis

Shock Produced by Failure of Cell Metabolism (Infection) — Patients with acute infectious diseases frequently develop the clinical picture of shock before they die Because the usual picture of congestive failure is absent, and because the circulation does not improve with the administration of digitalis frequently it is stated that the patient has peripheral circulatory failure or shock and that the circulation fails because of an inadequate venous return to the heart Observations were made on a group of patients with the clinical picture of shock produced by acute infections[1] By staying constantly present with all patients admitted with an overwhelming infection it was possible to obtain data before and during the period of circulatory failure When the course was unfavorable the circulation failed The patient became cold and pale and the pulse pressure narrowed At this time the physician in charge usually made the diagnosis of peripheral circulatory failure or shock Studies of the blood in such patients showed that the plasma volume was normal and that there was no evidence of hemoconcentration The vasomotor centers functioned normally because blocking the nerves to a cold extremity caused the extremity to become warmer These studies eliminated a decrease in blood volume or a failure in the vasomotor centers as the cause of the circulatory failure The possibility still existed that the shock might be caused by failure of the venous return from pooling of blood in dilated splanchnic veins If pooling of blood in dilated veins and a decrease in effective venous pressure in the right auricle were responsible for the circula

tory failure raising the venous pressure would improve the circulation The venous pressure was therefore recorded by inserting a needle in the external jugular or femoral veins Plasma blood and glucose solution then were given rapidly until the veins of the body were engorged and until the venous pressure was elevated The circulation did not improve demonstrating that the circula tory failure was not caused by an inadequate venous return The data sug gested that the heart was at least in part, at fault and that the circulation could not be restored to normal by raising the venous pressure Other studies have shown that none of the circulatory system functioned normally The infection had produced widespread metabolic disturbances in cell metabolism throughout the body and the cells were slowly dying The circulatory failure was econdary to a general failure in metabolism Treatment with transfusions and digitalis was usele s If the infection could be controlled the circulation improved If it could not be the patient died

This are picture of shock is seen not infrequently on the medical wards in patients with advanced liver destruction due to cirrhosis or metastases in pa tients dying with prolonged congestive failure and in patients who are dying from uremia or malignant hypertension Widespread areas of necrosi in any organ produce the same syndrome It is een on the surgical wards in the circulatory failure which occurs some days after a severe burn or postoperatively in patients who develop infection Unless the underlying metabolic defect can be corrected the patient dies Treatment directed towards increasing the filling pressure of the heart is without avail

Aub and his associates [9] have studied the toxic factor in traumatic shock in dogs They found that mu cles deprived of their blood supply frequently were infected with clostridia and that the edema fluid containing toxin from clostridia would produce shock when injected into normal dogs They conclude We think the evidence is quite convincing that infection is the so called toxic factor in traumatic hock in dogs The mechanism by which this toxin pro duces circulatory failure has not been defined When injected intramuscularly the toxin of the Welch bacillus (*Cl perfringens*) promptly produces a great deal of local edema but that of *Cl oedematiens* does not

Shock Produced by Changes in Tone of the Small Blood Vessels — Acute cir culatory collapse of reflex origin primary shock common faint with or without loss of consciousness produces the clinical picture of shock If the circulatory collapse is of short duration and sweating not excessive the extremities remain warm If it is more prolonged the extremities may become as cold as in any other form of failure of the circulation When the patient is first seen it may be impossible to decide whether this is a benign state or whether the patient is in extremis from blood loss pericardial tamponade or acute heart failure

Recent observations have been made on the state of the circulation during the acute circulatory collapse occurring in blood donors[18, 19] As blood is removed, the atrial pressure falls but it does not fall further when the collapse occurs The subject becomes very pale breaks out in a cold sweat and complains of nausea The arterial pressure falls precipitously and the pulse usually slows The cardiac output shows only a slight decrease or no decrease below the precollapse level

The circulatory failure is caused by a sharp fall in peripheral resistance, presumably by arteriolar dilatation It appears as if sensory stimuli from any efferent nerve or from the emotional control of thought may cause a sudden reflex arteriolar dilatation which results in a sharp fall in the arterial pressure If the patient is upright loss of consciousness will occur if the low arterial pressure is inadequate to maintain the cerebral blood flow against the force of gravity This type of collapse is benign in the recumbent position, because the overall tissue blood flow is not reduced

The factors responsible for the circulatory failure which can be produced by motionless standing in normal subjects after the ingestion of sodium nitrite[6] and in patients with acute infections and fatigue have never been completely determined How much of the circulatory failure is caused by pooling in veins whose tone has been decreased by disease or by drugs and how much is the result of arteriolar vasodilatation secondary to reflex stimuli induced by the upright position has never been demonstrated It is possible that both mechanisms are important

A marked decrease in arterial pressure without other evidences of circulatory insufficiency is seen after acute bouts of fever produced by malaria or the intravenous injection of typhoid vaccine[1]

Occasionally this occurs in other diseases as pneumonia It would appear that the infection has caused a loss of arteriolar tone and a lowering of the arterial pressure Certain drugs as alcohol seem to have a similar action Quantitative studies are needed in these patients before definite conclusions can be drawn

Anaphylactic shock causes a marked fall in arterial pressure and the clinical picture of shock It is not clear to what degree generalized interference with cell metabolism or hemoconcentration due to capillary damage produces the circulatory failure

IRREVERSIBLE SHOCK

As pointed out above any marked decrease in blood volume be it from loss of plasma because of local damage to capillaries from burns peritonitis or trauma or from loss of blood by hemorrhage or from loss of fluid by dehydration will

cause circulatory failure This circulatory failure occurs in the presence of a heart which is capable of normal function If the inadequate circulation lasts long enough the circulatory insufficiency is not easily reversed by transfusions and in time the condition becomes completely irreversible

Irreversible shock has puzzled clinicians and physiologists alike For a time it was believed that the capillaries throughout the body became more permeable because of circulatory insufficiency and that shock became irreversible because any fluid put into the vascular bed immediately leaked out This thesis seemed plausible because knowing that any injury to the capillaries by trauma burns or chemicals would cause the capillaries in the injured part to become abnormally permeable to protein it seemed logical that generalized circulatory failure might injure the capillaries throughout the body and cause the entire capillary bed even at a distance from the injury to leak protein freely This view was supported by the observation that complete ischemia to a part did cause local capillary damage and increased capillary permeability

Studies of the circulatory failure from trauma burns and infection have shown that capillaries away from the point of injury do not become abnormally permeable to protein because of prolonged circulatory failure[11, 1] Only capillaries at the site of injury leak protein freely Cells of blood vessels seem to be tougher than cells in certain other organs particularly the brain In generalized circulatory failure the central nervous system becomes depressed and the respirations stop before capillaries throughout the body are injured sufficiently to leak protein Similar observations have been made on the effects of oxygen lack on capillary permeability If the capillaries of a part are completely deprived of oxygen capillary damage results and capillaries in the anoxic part leak protein freely If an unanesthetized patient is studied it is found that progressive oxygen unsaturation of the arterial blood causes marked derangement in cerebral function before there is a detectable alteration in general capillary permeability[1]

Shock appears to become irreversible when prolonged circulatory insufficiency has caused permanent disturbances in the metabolism of cells throughout the body When the circulation is inadequate none of the cells of the body function normally In time these metabolic disturbances become irreversible and the cells begin to die At this time increasing the venous return to the heart and elevating the venous pressure does not restore the circulation to normal The situation is similar to that in circulatory failure caused by infection In so called irreversible shock the cells of the body are dying because of abnormalities in metabolism produced by prolonged circulatory failure In uncontrolled infections the cells are dying because the growth of bacteria has interfered with the enzyme systems of the cells In neither case will transfusions restore the circulation to normal

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Treatment of Shock

The proper treatment of a patient in shock depends upon the correct diagnosis as to the cause The treatment of the shock syndrome produced by heart failure massive pulmonary embolus pericardial tamponade and reflex arteriolar dilatation will not be discussed here

Shock Produced by a Decrease in Blood Volume — In patients who are in shock from hemorrhage restoration of blood volume by intravenous administration of physiological saline solution plasma or whole blood is life saving If hemorrhage has been massive the physiological saline solution will maintain the blood volume only while it is being administered rapidly Once the infusion has been stopped the blood volume will decrease rapidly because of depletion of the plasma protein by the hemorrhage If the hemorrhage is small while the circulation is being maintained by the intravenous infusion of salt solution the body will add sufficient protein to the plasma so that the blood volume does not decrease to the shock level when the infusion is stopped Plasma will restore the blood volume to normal and if the hemorrhage has been stopped it will remain in the vascular bed The treatment of hemorrhage by plasma causes anemia and if the hemoglobin falls below 7 gm per cent the anemia causes an added strain on the heart Blood is the ideal replacement fluid as it supplies both red cells and protein

Shock associated with injuries usually is accompanied by internal or external hemorrhage or hemorrhage into the tissues themselves Physiological saline solution plasma and whole blood are all useful in restoring the blood volume Whole blood is the ideal solution although physiological saline solution may be life saving while blood is being obtained Again plasma is superior to salt solution but will in time lead to the complication of anemia If bleeding is taking place in the tissues a light pressure bandage may decrease the rate of loss of blood from the vascular bed

Shock produced by burns and by certain injuries in which the tissues have been deprived of blood for long periods of time and by fulminating peritonitis is characterized by the loss of plasma from the vascular bed The loss of plasma may be lessened in some instances by the application of external pressure by appropriate bandaging

Plasma is the ideal replacement fluid although in the case of burns a considerable quantity of red cells may have been destroyed also In severe burns whole blood may be alternated with plasma once the original hemoconcentration has been overcome by the use of plasma As the fluid lost into the tissues in the burned areas contains large amounts of electrolyte approximately one-half of the fluids given intravenously should consist of physiological saline solution or

The Relationship between Reversible and Irreversible Shock

The relationship between shock which responds to therapy, and irreversible shock may be illustrated by the description of the clinical course of a patient with a perforated peptic ulcer who enters the hospital in shock 12 hours after perforation He is pale sweating mentally confused and has a low arterial pressure with a narrow pulse pressure Examination of the blood will show marked hemoconcentration and a striking decrease in plasma volume and the quantity of circulating plasma protein The circulation has failed because the blood volume has decreased to so great an extent that the venous return to the heart is inadequate The heart is capable of pumping blood but it is not receiving the blood to pump This can be proven by giving a large infusion of plasma As the plasma volume rises the venous return to the heart increases, and the circulation rapidly returns to normal The patient is dramatically improved The cause of the hemoconcentration and the decrease in the quantity of plasma in the blood stream is not difficult to find The abdomen contains several liters of fluid which has a protein concentration of about 4 grams per cent The chemical irritation caused by the leakage of gastric juice into the peritoneal cavity has altered the permeability of the capillaries and almost pure plasma has leaked from the blood stream into the peritoneal cavity

The patient is taken to the operating room and the perforation is closed The condition of the patient remains good for twenty four hours then evidence of generalized peritonitis appears and the subsequent course is progressively downward Plasma transfusions are continued but the circulation again fails The patient is once more pale and cold with a weak thready pulse but now there is no hemoconcentration and the plasma volume is normal Further transfusions are of no value because the circulatory failure is caused not by a decrease in blood volume but by alterations in cell metabolism produced by the infection

Multiple Factors in the Production of Shock

For sake of clarity of presentation the various mechanisms which may produce the clinical picture of shock have been described separately In practice a patient may be in shock as the result of two or more of the disturbances in function which have been discussed Crushing injuries which cause hemorrhage into the tissues frequently are associated with disturbances in cell metabolism secondary to infection in the part or to tissue necrosis Reflex arteriolar dilatation from sensory or psychic stimuli is very common in patients with circulatory insufficiency caused by a small blood volume Arteriolar dilatation caused by the ingestion of alcohol is a frequent complication in injured persons

cular di ease and necrosis of neoplastic tissue the disturbances in cell metabolism usually are irreversible

Digitalis is not beneficial in these patients Generally vasoconstrictor drugs as ephedrine and paradrinol are not u eful These sympathomimetic drugs may be beneficial however, in patients in whom the chief disturbance is a sharp fall in arterial pressure and the tissue flow is well maintained as shown by a warm, flu hed skin

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preferably of a mixture of two thirds physiological saline solution and one third sixth molar sodium lactate solution Treatment is guided by the hematocrit reading and the hemoglobin concentration

Because of the adverse effect of infection on the circulatory system and metabolism in general prophylactic therapy with sulfadiazine or penicillin often is indicated If the urinary output is decreased, as it frequently is, penicillin is the drug of choice

The prevention of pain by the use of adequate splints and by morphine is of great importance in the prevention of reflex circulatory collapse

Patients in shock due to injury or loss of blood tolerate the upright position poorly The head and trunk certainly should not be raised, and they probably benefit by elevation of the foot of the bed

Patients in shock frequently have low rectal temperatures Most authorities advise applying warm blankets and hot water bottles The question has been raised as to whether heating the body and producing vasodilatation has a deleterious effect on the patient in shock whose circulation has failed because of a small blood volume The point usually is not of practical importance because in most instances the blood volume is increased by the intravenous administration of fluid while heat is being applied

In severe injuries burns and infections there is a markedly negative nitrogen balance and malnutrition develops rapidly Unless attention is paid to this complication in the first few days the patient s general condition deteriorates and he is much more prone to develop circulatory failure A high protein high vitamin diet should be given and if the patient does not tolerate it, amino acid solution should be given intravenously

Vasoconstrictor drugs as ephedrine and paredrinol have not proven useful The administration of oxygen and adrenal cortical extract has been recommended but neither has been shown to be useful in the treatment of patients with this type of shock

Shock Produced by Disturbance of Cell Metabolism —If infection is the cause of the disturbance in cell metabolism, controlling the infection by chemotherapy by the use of serum or by surgical drainage will reverse the process and cure the shock If the infection is complicated by dehydration the intravenous administration of physiological saline solution will cause a striking improvement in the circulation If dehydration has been prevented and the circulation fails transfusions of blood plasma and other solutions are without avail When the infection has persisted for a considerable time the use of a high protein high vitamin diet and, if necessary the parenteral administration of amino acids are indicated

In shock caused by liver disease renal failure wide spread obliterative vas

CHAPTER XIV

DISEASES OF THE BLOOD VESSELS

By DUNCAN GRAHAM

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December 1 1945

PART II

Diseases of Veins

Introduction

The heart, arteries capillaries and veins which constitute the circulatory system normally function as a co ordinated unit to maintain a circulation of blood adequate to meet the needs of the tissues of the body for oxygen and nutriment and to remove the waste products of metabolism In disease a disorder of one part of the system tends to affect the functional efficiency of other parts Disease of the heart with failure often results in a breakdown of the whole system and must be excluded before attributing the cause of a disturbance in circulation to another part of the vascular system

In the past, clinicians have paid too little attention to the role of the capillaries in disease of the peripheral blood vessels Disorders of arterial origin always affect the capillary system—terminal arterioles capillaries and venules—and the visible circulatory disturbances present are in large part, due to abnormal alterations in the blood flow through this system Further interference with the return of blood to the heart from disease of the veins may disturb the capillary circulation Then too the capillaries themselves may be the primary site of disturbances in the circulation These facts must be borne in mind in any attempt to diagnose the primary origin of disturbances of the circulation whether of heart, arteries capillaries, or veins

Anatomy and Physiology

The *arteries* of the body differ in size, structure, and their chief functions They may be divided into three groups (1) the large or elastic arteries—aorta pulmonary innominate, subclavian common carotid, and common iliac, (2) the medium or musculo elastic arteries—carotid axillary brachial radial iliac femoral popliteal and tibial (3) the small muscular arteries and arterioles constituting the intimate vasculature of the internal organs skeletal muscles and skin The walls of all arteries are composed of three layers tunica intima tunica media and tunica adventitia The intima consists of an inner lining of endothelial cells a subendothelial layer of delicate connective tissue (except in the smallest arteries and arterioles), and an elastic layer—the internal elastic lamina The media contains elastic and muscular tissue and the relative proportions of each vary with the size of the artery The larger arteries are rich in elastic tissue and relatively poor in muscular tissue and

We have a propulsive organ, the heart, a distributing organ, the system of arteries, an organ for interchange of substances between the blood and the tissues, the capillaries, an organ for collecting the blood and carrying it back to the heart, the venous system It is evident that the organs of propulsion, distributing and carrying back are all subservient to the function of exchange carried out in the capillaries and, though of course each of the great organs is absolutely necessary for the functioning of the whole, it will be difficult to challenge the proposition that the capillaries constitute the most essential part of the whole circulatory system (Krogh[1] *The Anatomy and Physiology of Capillaries*)

tenance of the local temperature in distal parts of the extremities on exposure to extremes of cold or heat [5]

The *capillaries* form a fine meshwork of tiny vessels, four to twelve microns in diameter between the terminal arterioles and the venules They are endothelial tubes formed by a continuation of the endothelial lining of the arterioles From the smallest arteries to arterioles the layers of circular muscle fibers in the media decrease in number until a single layer of muscle cells encircles the precapillary arterioles On the outer surface of the capillaries this layer is replaced by scattered cells with fine processes which surround the endothelial tube Rouget[6] who first described them in 1873, and later Vimtrup[7] considered them responsible for capillary contraction, but Clark and Clark[8] believe these cells are derived from connective tissue and are not active in producing capillary contraction Although the origin of these cells and their relation to capillary contraction remain undetermined, it is known that the capillaries possess inherent tone and are capable of contracting and dilating quite independently of the arterioles [1,9] The capillaries are supplied with sympathetic nerve fibers but have no sensory innervation[3] On the venous side capillary loops unite to form venules which again unite to form small veins The venules are wider than capillaries but similar in structure and function From functional and clinical standpoints it seems best to include the precapillary or terminal arterioles, capillaries and venules in referring to the capillary system

The *veins* are larger in diameter than the corresponding arteries Their walls have three coats like the arteries but are much thinner due chiefly to the smaller amount of elastic and muscular tissue in the media The amount of muscular tissue in the media is greater in large than in medium-sized veins and greater in the veins of the lower limb than in those of the upper The adventitia is much thicker than the media and consists of a loose connective tissue with elastic fibers and longitudinal bundles of muscle fibers adjacent to the media Veins are supplied with semilunar valves formed by a folding of the intima These valves are located just distal to the entrance of a branch vein just distal to the point where it empties into a larger vein and permit blood to flow towards but not away from the heart The veins like the arteries are innervated proximally by fibers from adjacent sympathetic ganglia and distally from peripheral nerve trunks They possess vascular tone dependent upon the integrity of the sympathetic nervous system but also upon circulating hormones such as epinephrine

the converse is true of the smaller arteries and arterioles The adventitia or external layer is composed of connective tissue which contains elastic fibers and scattered bundles of muscle fibers, nerves and small blood vessels, vasa vasorum, and branches of lymphatic vessels ramify in the adventitia The vasa vasorum, which nourish the artery, penetrate the outer part of the media but do not reach the intima

All arteries are supplied with vasomotor nerves belonging to the sympathetic nervous system, and the arteries of the upper and lower limbs have also a sensory nerve supply from somatic nerves The vasomotor nerves are supplied in two ways by a proximal innervation from adjacent sympathetic ganglia and by a distal sympathetic and sensory innervation from neighboring somatic nerves Fibers from adjacent sympathetic ganglia provide a direct nerve supply to the entire aorta and its main branches [3] These fibers form periarterial plexuses which continue along the carotid and vertebral arteries to the head, to the subclavian artery, along branches of the aorta to the abdominal viscera, and along the iliac to the femoral artery of the lower limb Under normal conditions the proximal innervation of the large arteries plays no part in the nervous control of the circulation in the limbs In acute occlusion of the subclavian aortic bifurcation, or iliac arteries from embolism, the proximal innervation causes vasoconstriction of arteries arising proximal to the occlusion and forming the collateral circulation to tissues distal to the occlusion, and may be a factor in the production of the initial pain often present at the site of embolic occlusion [4] Sensory and sympathetic fibers from somatic nerves overlap the proximal innervation and supply the axillary artery in the upper limb, the distal part of the femoral in the lower limb, and the more distal medium sized and small arteries and arterioles in both limbs These nerve fibers are distributed at intervals along the peripheral arteries[3] but form a periarterial plexus which is continuous throughout the length of each vessel Sensory fibers, which predominate in the larger arteries of the limbs, terminate in fine nerve endings in the adventitia Sympathetic fibers almost entirely vasoconstrictor in function, predominate in the small arteries and arterioles and penetrate the media to end around muscle cells

In certain areas of the limbs—ends of the digits palms of the hands and soles of the feet—blood may pass directly from the arterioles to the veins through arteriovenous anastomoses [5a] The media of these anastomoses is very muscular and richly innervated They play a dominant role in the regulation of the body temperature and the main

level despite wide variations in the environmental temperature The head and trunk play a minor role in the exchange of heat between the whole body and its environment Loss of heat from the extremities occurs chiefly through arteriovenous anastomoses in the hands and feet, mainly the digits and especially the fingers [6] As skin temperature depends on heat brought by the blood stream and loss of heat from the surface of the skin, the temperature of the skin is an indication of the rate of blood flow through cutaneous vessels which is determined by the degree of contraction or dilation of the smallest arteries and arterioles At different environmental temperatures the skin of the head trunk and proximal parts of the limbs shows minor changes in temperature when the hands and feet—especially the digits—show marked changes If the whole body is exposed in a room temperature of 30° to 35° C (86° to 95° F), the surface skin temperature in all parts of the body is between 33° and 36° C (91 4° to 96 F)—the maximum vasodilation level In a room at 20° C (68° F) the skin temperature of the head trunk and proximal parts of the limbs is close to the maximum vasodilation level but that of the fingers and toes is 3° to 7 C lower than the trunk, with the toes 2° C lower than the fingers [10, 11] In a cooler environment, 18° C (64 F), the skin temperature of the head trunk and proximal parts of the limbs shows little change but the temperature of the fingers falls 7° C or more and that of the toes to approximately the environmental temperature When the environmental temperature is raised from 18° C vasodilation occurs first in the fingers and later in the toes [11]

These observations offer an explanation for the feet always feeling cooler than the hands under ordinary environmental conditions and demonstrate the importance of the distal parts of the limbs especially the digits in the regulation of body temperature If the environmental temperature affects the temperature of the circulating blood by 0 01 C this change reacts on the heat regulating center in the hypothalmus a fall in blood temperature causing vasoconstriction of cutaneous arterioles to conserve heat, and a rise in temperature increasing vasodilation for the dissipation of heat from the acral parts [1] This mechanism comes into play if a large surface of the body is exposed to moderate heat or cold or one extremity to more extreme heat—43° to 45° C (109 to 113° F)—or to more extreme cold—14° C (57 F) Warming the trunk [13] or immersing one upper limb in water at 43° C [14] and measuring the surface skin temperature of the toes is a method used to determine the degree of vasodilation present in a lower limb suspected of obliterative vascular disease

Functions and Control of the Peripheral Blood Vessels The whole purpose of the arteries is to distribute a continuous flow of blood to the arterioles in quantities adequate to meet the needs of the tissues of the body The large arteries act as an elastic reservoir Their elastic structure allows them to distend upon receiving blood with each systole of the heart and to return to their normal size during diastole Thus the intermittent flow of blood from the heart into the aorta is converted into a continuous flow to the arterioles which distribute it to the capillary system The medium sized arteries aid in this process, but their main function is the distribution of blood to the smallest arteries and arterioles Arteriovenous anastomoses of the acral parts and the strong arterioles of the cutaneous vessels and splanchnic area play an important role in the regulation of the systemic blood pressure and the temperature of the body They act as 'stop cocks' and control the outflow of blood into the capillary system according to the physiological needs of the tissues under conditions of rest and of increased activity, of over cooling or over-heating With exercise the capillaries and arterioles in skeletal muscle dilate and those in the splanchnic area and skin contract In a similar fashion, alterations in the blood supply of the skin, more particularly of the hands and feet, occur for the maintenance of a normal body temperature When the external temperature is low the cutaneous vessels contract to diminish the loss of heat from the body, the converse occurring with high external temperatures

These cutaneous vascular reactions are controlled from the vasomotor center in the hypothalmus through sympathetic nerves supplying the peripheral blood vessels Efferent sympathetic vasoconstrictor fibers from the vasomotor center exercise a continuous control over the tone of the arterioles Through this control of blood flow in the smallest arteries and strong arterioles the total blood volume, the systemic blood pressure, and the temperature of the body are maintained at fairly constant levels despite wide variations in the supply of blood to different parts of the body at different times The height of the blood pressure depends on the cardiac output and the peripheral resistance in the tonically contracted strong arterioles in the splanchnic area and skin Afferent impulses from the carotid sinus and aortic nerves, through their influence on the vasomotor and cardiac centers and on epinephrine secretion provide a reflex nervous control of the systemic blood pressure, maintaining it within relatively narrow limits

The extremities, especially the acral parts play an important role in the control of body temperature which is maintained at a fairly constant

crease in blood flow necessary to meet tissue requirements amounts to twenty to thirty times the resting flow

The part played by the sympathetic nerves in the control of the circulation in skeletal muscle is not fully known Barcroft *et al*,[6] using the plethysmograph observed that warming the body or blocking the motor nerves to the forearm doubled the blood flow in the forearm and that this effect was abolished by sympathectomy They concluded that the increase in blood flow in the forearm must be due to the release of sympathetic vasoconstrictor tone in blood vessels which are probably in the skeletal muscles Later Barcroft *et al*[1] investigated the effect of the release of vasoconstrictor tone on the blood flow of active muscles in the forearm and calf and found that the resting blood flow was doubled but that the post exercise blood flow changes before and during the release of sympathetic vasoconstrictor tone were the same They concluded that the vasomotor center had no effect on the circulation changes taking place in the forearm and calf during or after muscular activity

From these investigations it may be accepted that the blood vessels responsible for doubling the blood flow in forearm and calf after indirect heating are supplied by sympathetic vasoconstrictor fibers but it does not appear to be proven that the vessels responsible for the increase in blood flow are in the skeletal muscles or are vessels forming the collateral circulation for Shepherd[m] found a like increase in blood flow in the calf after occlusion of the femoral artery In any case it seems clear that the release of sympathetic vasoconstrictor tone by sympathectomy can have little effect on the relative ischemia causing intermittent claudication in obliterative vascular disease of the extremities for the blood flow necessary to meet tissue requirements in moderate exercise is at least ten times the resting muscle blood flow

In experiments in hemorrhage Barcroft *et al*[3] observed an increase in blood flow of the forearm of a subject during a faint They showed that the increased blood flow was mediated by sympathetic vasodilator fibers These like similar vasodilator fibers to cutaneous vessels play no significant role in the nervous control of the circulation in the extremities

The chief function of the capillary system is the interchange of substances between the circulating blood and the tissues The capillary *blood pressure in the arteriolar limb of the capillary is higher and in the* venous limb lower than the osmotic pressure[4] This favors the transudation of substances from the blood in the arteriolar end and the absorption of tissue products in the venous end The caliber of the capillaries in skin and skeletal muscle is regulated chiefly by local metabolites and

In addition to this central sympathetic control of body temperature there is also a local control. If the limbs are exposed to cold, all the cutaneous vessels—arteries, arterioles, capillaries and veins—contract to conserve body heat. This contraction is a direct effect of cold, for it occurs after sympathectomy and the release of vasoconstrictor tone.[9]

Vasodilation or vasoconstriction induced in the digits of one extremity by warming or cooling another is referred to as indirect or reflex vasodilation or vasoconstriction.[15] This reflex response is dependent upon the integrity of the sympathetic nervous system, since it is absent in a sympathectomized limb.[13] The chief factor in its causation is an increase or decrease in the temperature of the blood returning to the vasomotor center in the hypothalmus from the immersed limb. But afferent nervous impulses also play a role, for cold applied to an extremity with the circulation occluded results in vasoconstriction in the other extremities.[13] The immersion of one limb in water at 43° to 45° C. raises the surface skin temperature of the acral parts of other limbs but causes little change in the skin temperature of the proximal parts. If the immersed limb is exposed to a higher temperature in the same manner, dilation of the cutaneous vessels of proximal parts occurs. This has been shown to be due to sympathetic vasodilator fibers,[16] but they play no significant role in the nervous control of cutaneous vessels.

Although the cutaneous vessels of the hands and feet, especially the arteriovenous anastomoses, through the release of vasoconstrictor tone play a dominant role in the regulation of body temperature, alteration in blood flow through skeletal muscles plays little or no part. Grant[17] has shown that the greatly increased blood flow in the skeletal muscles of the forearm after exercise is independent of the sympathetic nerves, being similar in normal and sympathectomized limbs. He concluded that the increased blood flow from exercise was due to local metabolites from the active muscle fibers, as first suggested by Gaskell.[18] The increased blood flow raises the temperature of the exercised muscles but the heat is transmitted to the overlying skin and does not affect the body temperature unless the exercise is strenuous.[17]

It is now generally accepted that the blood flow in skeletal muscle during muscular exercise is regulated by local metabolites. These accumulate during activity and cause a dilation of the rich muscle capillary bed. The dilatation of the capillary bed is accompanied by an increase in the circulation rate and a diversion of blood from less active parts of the body to the exercised muscles.[19] During muscular activity the in-

the flow of blood forward but not backward and by contractions of the skeletal muscles which compress the veins and propel the blood towards the heart The valves and the muscles function as a pump in lifting the column of blood into the veins of the abdomen In the lower extremity there are two systems of veins the deep and superficial, connected by communicating veins The larger and more numerous deep veins are surrounded and supported by the skeletal muscles The superficial veins lie imbedded in the subcutaneous tissue between the skin and the fascial aponeuroses and the support of their walls is dependent on the elastic skin and subcutaneous tissue Valves in the superficial and deep veins are placed at intervals from the periphery to the external iliac Valves in the communicating veins permit the flow of blood from the superficial to the deep system but not a reverse flow With contraction of the skeletal muscles as in walking there is direct compression of the deep veins and an indirect and less effective compression of the superficial veins which propels the blood forward the valves preventing a backward flow on muscular relaxation The subatmospheric pressure within the thorax particularly during inspiration dilates the intrathoracic veins and sucks blood from the abdominal veins and the downward pressure of the diaphragm and the support of the abdominal muscles compresses the abdominal veins and augments the venous flow from the abdomen to thorax

PART I

DISEASES OF ARTERIES

General Clinical Considerations of Arterial Lesions

Arterial lesions with the exception of such acute conditions as rupture acute inflammation, or sudden occlusion from embolism or thrombosis which are considered later are seldom the direct cause of the local signs and symptoms present in arterial disease Local clinical manifestations are for the most part due to the effects of a disturbance in the circulation of blood through vessels distal to the site of the primary arterial lesion For this reason disturbances in the capillary and venous circulation are also present and may dominate the clinical picture If one excludes lesions of the coronary arteries which affect the heart and thereby the cardiac output, circulatory disturbances from arterial disease usually are confined to a particular area or areas and are seldom general

varies according to the metabolic needs of the tissues Metabolites accumulate in the tissues in nutritional need and anoxia, in trauma, ischemia and inflammation and cause a dilatation of the capillary system and increased blood flow Injury to the skin from various agents—mechanical chemical or thermal—causes the release of an H substance probably histamine, which by direct action on the capillaries causes a local dilatation (red reaction) and often swelling (wheals) and stimulates the sensory nerves to the skin and through a local sensory axon reflex, causes a dilatation of the arterioles (flare)—the triple response of Lewis[8] The increased blood flow not only aids in removing injurious substances thereby preventing more serious damage to the local tissues, but serves to promote healing of the injured part The flare does not develop if the sensory nerves to the skin have degenerated

It is well known that if the circulation to a limb is arrested by a tourniquet and then released a cutaneous hyperemia develops This reaction known as reactive hyperemia has been shown by Lewis and Grant to be due to the accumulation of local metabolites in the skin during the period of arrest of blood flow and to be independent of any nervous influences The duration of the reaction is usually one half to three quarters of the ischemic period The flushing of the skin causes no increase in body temperature

Apart from pigmentary effects the state of the capillary circulation and the hemoglobin content of the blood determine the color and tint of the skin The depth in color of the skin depends upon the percentage of hemoglobin and its tint on the rate of blood flow The pink tint of arterial blood is due to oxyhemoglobin, the bluish tint of venous blood to reduced hemoglobin resulting from oxygen given up to the tissues in the passage of blood through the capillary system The slower the flow, the more reduced the hemoglobin giving a bluish color to the skin—cyanosis

The chief function of the veins is the collection of blood from the capillary system and the carrying of it back to the heart The slightly higher pressure in the capillary system from the contraction of the left ventricle (*vis a tergo*) causes the blood to flow into the veins In the erect position gravity aids the return of blood in veins above the level of the heart but opposes the flow in veins below the heart This opposing effect of gravity on venous return is therefore greater in the lower than in the upper extremity and accounts for the greater frequency of venous disturbances in the lower extremity Normally the gravity effect is overcome by valves in the veins of the extremities which permit

The two important clinical manifestations of abnormal local vasoconstriction and vasodilatation in the acral parts are abnormal changes in the temperature and tint of the skin Coldness of a hand or foot indicates a slow or deficient blood flow through the arterioles from vasoconstriction, and an increased temperature, an accelerated flow from vasodilatation Color changes in the skin—pallor cyanosis, and rubor—indicate disturbances in the capillary circulation associated with abnormal vasoconstriction or vasodilatation of the proximal arterioles or arteries Pallor or blanching is a sign of emptiness of the capillaries with little or no blood flow through the arterioles In local cyanosis there is a slow passage or stasis of blood in the capillaries with a marked slowing or cessation of blood flow through the arterioles The result is that more oxygen is given up by the blood in the capillaries to the surrounding tissues and the part becomes bluish in color Attacks of coldness with pallor or cyanosis in a part are followed by the development of rubor or redness With relaxation of the arterioles bright red blood enters the capillaries and the skin becomes red and warm The color and temperature of the affected area gradually return to their normal condition until another attack occurs In the pallor stage the part may feel numb, with the development of rubor, numbness is replaced by tingling and burning sensations and pain may be present Lewis [8] has given the following useful classification of the temperature and color changes occurring in the skin with brief but pertinent descriptions of their significance

Warm Pale Skin This is a skin through which blood flows rapidly for many minutes It is warm because flow is fast pink because of the abundant supply of fully oxygenated blood and pale because the skin is well nourished and minute vessel tone is therefore high

Warm Deeply Colored Red Skin Such skin has been irritated by heat or otherwise it is in a state of inflammation, or it is skin in which arterial vasodilatation has recently been brought about through nervous channels or by means of drugs such as amyl nitrite

Warm Deeply Colored Cyanosed Skin Unless the blood pigments are abnormal this is skin to which the supply of blood is imperfect and which has been made warm by external heating

Cold Pale Cyanosed Skin This is skin to which the blood flow is very slow or absent If the tint of the cold skin is violaceous or if the skin is blanched the circulation to it is absent and has been arrested in it for many minutes Minor grades of cyanosis are as previously stated of much less significance

in nature Circulatory disturbances of internal organs can only be diagnosed from the presence of signs and symptoms of impairment of function in the organ or organs affected, e g the heart or brain in coronary or cerebral arteriosclerosis In the extremities the diagnosis of arterial disturbances is less difficult The part can not only be inspected and the vessels palpated but the nature and cause of the clinical manifestations in peripheral vascular disturbances are better understood than circulatory disturbances of the internal organs

Classification of Arterial Lesions

Vascular disturbances of arterial origin may be separated into two main groups (1) functional—due to thermal, mechanical, chemical, or nervous influences affecting the caliber of the smaller arteries and arterioles, (2) organic or obliterative—due to structural changes in the larger arteries causing partial or complete obstruction to the blood flow distal to the site of the lesion As functional disturbances are commonly present and often are early manifestations in organic arterial disease, and as structural changes may develop in the later stages of functional arterial disease, no hard and fast line can be drawn between these two groups of vascular disturbances

Functional Arterial Disturbances

General Considerations

Functional arterial disturbances are essentially disorders of the smaller arteries and arterioles due to abnormal vasoconstriction or vasodilatation A persistent abnormal constriction or increased tone of the arterioles concerned in the maintenance of the peripheral resistance of the circulation occurs in essential hypertension It may exist for a long period, even years in the benign form of essential hypertension without the development of any significant local or general circulatory disturbance The same is true in persistent hypotension On the other hand, a sudden alteration in the tone of the strong arterioles causing an abrupt change in the systolic blood pressure results in an acute general circulatory disturbance However local rather than general functional arterial disturbances, which are unaccompanied by significant alterations in blood pressure are much more common Usually they are characterized by abnormal local vasoconstriction or much less often by vasodilatation of the peripheral arteries, chiefly of the hands and feet

result The local damage to tissues from freezing is aggravated by excessive warmth during the stage of recovery

These vascular responses following frostbite—the triple response of Lewis[9]—are due to the release in the skin of an H substance, probably histamine which by indirect action through a local sensory axon reflex causes a dilatation of the arterioles with reddening of the part and by direct action on capillaries causes dilatation and increased permeability of their walls resulting in edema or, with more severe injury, blisters vesicles and even hemorrhage A similar type of reaction follows injury to the skin from a variety of agents mechanical chemical, and electrical If the sensory nerves to the skin have degenerated dilatation of the capillaries and edema develop with frostbite but increased blood flow from dilatation of the arterioles is absent This probably accounts for the development of so called trophic disturbances with lesions causing degeneration of the peripheral sensory nerves [9] A permanent dilatation of the capillaries particularly of the cheeks may result from repeated exposure to cold, it is due to a loss of capillary tone A similar result may follow the exposure of the skin to X ray

A history of cold hands and feet often with excessive perspiration occurring chiefly among women is not uncommon These individuals usually are underweight are often of a nervous type contract infections easily and often suffer from a chronic focal infection—teeth tonsils nasopharynx sinus etc Their extremities, particularly the digits are cooler than normal but show no significant color changes other than a slight cyanosis

In a certain group of individuals often of the type mentioned above exposure to moderate cold produces more abnormal peripheral vascular disturbances With some moderate cold causes attacks of pallor and cyanosis of the fingers and less often the toes—*Raynaud's phenomenon* in others the hands from a little above the wrists to the finger tips are bluish red in color cold and clammy—*acrocyanosis* In cold, damp climates but rarely in cold dry climates exposure to moderate cold particularly in young girls may cause itching burning and swelling of the hands and feet—*chilblain*—or tender purple and red swellings on the lower part of the leg—*erythrocyanosis* In rare cases exposure to cold may cause not only a more marked local but even a general reaction [10] Exposure to cold wind or placing the hand in cold water may cause redness itching and burning and swelling of the skin—*urticaria*—or the drinking of cold water may result in swelling of the mucous membranes of the throat with difficulty in breathing or a severe constitutional

Cold Deeply Colored Cyanosed Skin This is skin in which the circulation is very slow and in which blood flow has been failing for a long time or in which there is a process of low-grade inflammation

Cold Deeply Colored Red Skin If the skin is sufficiently cold, 10° C (50° F) or less the blood will not part with its oxygen but the minute vessels are damaged and dilate and thus the skin becomes bright red in color although the blood flow through it may be small

As exposure to cold is a common inciting factor in the causation of local peripheral vascular disturbances, a consideration of the normal vascular responses to cold is important Normally, considerable alteration in the external temperature may take place without significant changes in the color of the skin, but frequent exposure to cold or damp and wind in cold climates may result in the development of abnormal color changes in the hands and feet, ears and nose The stimulus of cold by reflex action through the central nervous system causes an immediate but transient general vasoconstriction of the cutaneous blood vessels, with paling of the skin If the exposure to cold is prolonged and the temperature of the circulating blood is lowered, a persistent general vasoconstriction of the skin develops due to the action of cool blood on the central nervous mechanism [1] Cold also acts directly on the vessels of the skin causing vasoconstriction Upon exposure to moderate cold, the arteries, capillaries, and veins are constricted but redness soon develops and the part becomes warmer due to a dilatation of the arterioles [1] in the exposed region In the hands and feet an increased blood flow through arteriovenous anastomoses is an important contributing factor [5a] This normal vascular response to moderate cold not too prolonged, serves to protect the tissues of the exposed part from injury in cold weather [2]

If exposure to cold is prolonged at temperatures below 15° C (59° F) but above freezing, pain is experienced and the exposed part becomes swollen following vasodilatation but soon returns to normal When the skin is exposed to temperatures below freezing and becomes frozen the exposed part becomes waxy white painful and then numb After entering a warm room the frozen area becomes bright red warmer, and swollen Numbness is replaced by tingling itching burning sensation and throbbing This reaction to frostbite of the first degree gradually subsides In second degree frostbite swelling and itching of the part are more marked, blisters or vesicles develop and the skin is red or purplish in color If the exposure to cold is more severe necrosis of tissues may

fined largely to the skin Raynaud recognized that cold was of importance in provoking the attacks and that the obstruction to the blood flow was on the arterial side and due to spasm He considered the vascular disturbances as due to a vasomotor neurosis a theory that has been generally accepted and that has led to the classification of the syndrome as a vasomotor or trophic disorder

Many years later Hutchinson[31] pointed out that the vascular disturbances in the malady described by Raynaud might occur in different conditions and contended that Raynaud s syndrome was not a disease entity He proposed the term 'Raynaud s phenomenon' rather than Raynaud s disease for disorders characterized by attacks of intermittent pallor or cyanosis in the digits With a better understanding of peripheral vascular disturbances it is evident that Raynaud s phenomenon may develop as a secondary manifestation in primary organic vascular disease of the extremities such as thromboangiitis obliterans in scleroderma in certain cases of cervical rib, and from trauma as in workers with vibrating tools It is necessary therefore to distinguish between primary and secondary Raynaud s phenomenon

Primary Raynaud's Phenomenon (Raynaud's Disease) It is now generally accepted that the vascular disturbances in Raynaud s disease are of arterial origin and result from spasm of the digital arteries induced by cold or cold and emotion Opinion as to the primary cause of the spasm is diverse Lewis[3] has shown that attacks of cyanosis can be induced in affected fingers by direct exposure to cold after an anesthetic block of the local nerve supply or after postganglionic[33a] or preganglionic sympathectomy[33b] From these and other carefully controlled investigations Lewis concluded that spasm is not due to abnormal vasomotor impulses but to a local vascular fault which manifests itself by a local hypersensitivity of the digital arteries to cold Since then others have applied his methods to test these two opposing views of Raynaud and Lewis as to the primary cause of spasm

Morton and Scott[34] agree with Lewis that the essential abnormality in Raynaud s disease is a local hypersensitivity of the peripheral arteries to cold They believe, however that vasoconstrictor influences are powerful in bringing on and keeping up attacks and that their removal by sympathectomy may be effective in prevention Simpson, Brown and Adson[35] are of the opinion that the primary cause of spasm is an abnormality of the sympathetic nervous system but they admit that in severe cases of Raynaud s disease an abnormal reaction of the arteries to cold may be present Gask and Ross[36] who studied the effect of sympathec-

reaction causing collapse—*giant urticaria* or *angioneurotic edema* This is an allergic type of reaction which may also result from exposure to heat light, etc These different cutaneous reactions represent different types of vascular responses in the peripheral circulation to a common inciting factor exposure to cold They vary in severity in different individuals and the same individual may show more than one type of vascular response

Clinical conditions in which these types of peripheral vascular disturbances occur usually have been classified in textbooks under diseases of the nervous system as an *angioneurosis* or a *vasomotorneurosis* or, if nutritional changes are present as a *trophoneurosis* The common belief has been that they result from a disturbance of the vasomotor or sympathetic nerves but more recent work tends to show that, in some instances at least, influences acting apart from the nervous system must be responsible It seems clear that primary disturbances in the capillary system (terminal arterioles capillaries and venules) are of local origin and not dependent upon local or central nervous control Local dilatation of the arterioles following injury to the skin is absent if the peripheral sensory nerves have degenerated but is present with degeneration of the sympathetic or motor nerves Cooling of the body, emotional stimuli like fear, or strong sensory stimuli like pain cause a central reflex constriction of the peripheral vessels, but this reaction occurs in all normal individuals It has been generally accepted that the abnormal vasoconstriction occurring in Raynaud s disease is of vasomotor or sympathetic origin but the recent work of Lewis and his associates which will be discussed in more detail strongly suggests that the vascular reaction is of local arterial rather than of nervous origin In the light of our present knowledge of the mechanism of these different vascular disturbances it would seem more appropriate to classify them under diseases of the vascular than of the nervous system

Vasospastic Disturbances

Raynaud's Phenomenon In 186 Raynaud[30] published a monograph on local asphyxia and symmetrical gangrene of the extremities calling attention to the occurrence of gangrene without organic vascular occlusion The clinical syndrome was characterized by recurring attacks of blanching or 'dead fingers or by attacks of cyanosis of the digits of the hands and feet followed, after many recurrences by the development of superficial gangrene of the digits having a symmetrical distribution and con

The disease is not common nor is it peculiar to any nationality Monro[40] and Brown[11] both found about one case occurring among 3,000 patients Brown estimates that o per cent of peripheral vascular disturbances belong to the functional group and that 44 per cent of vasospastic disturbances are of the Raynaud type

Symptoms usually begin in the second and third decades of life, rarely before ten years or after sixty Women are affected much more commonly than men In Brown s series 90 per cent were women

More than one member of a family may be affected The familial incidence of the disease probably is greater than is generally realized[59]

Cold is generally accepted as the common inciting factor of attacks A hypersensitivity to the stimulus of cold manifesting itself by spasm of the digital arteries and arterioles is always present The inherited sensitivity present in subjects of hay fever, asthma, and urticaria supports the premise that in Raynaud s disease vascular sensitivity to cold may be an inherited factor

Some observers have stated that the malady frequently occurs among neuropathic subjects and that in them emotional stimuli may provoke an attack As pointed out by Lewis[59] it seems likely that in attacks occurring during an emotional upset two factors are responsible viz partial spasm of the arteries due to the direct action of cold plus increased vasomotor tone from emotional stimuli These two factors acting together produce a cessation of blood flow in the digital arteries with discoloration of the digit Lewis is of the opinion that emotional stimuli alone cannot produce an attack with discoloration

Character of abnormal vascular response The malady is characterized by intermittent attacks of discoloration of the digits precipitated by exposure to cold In mild cases recovery from each attack is complete, the pale or cyanosed part becoming first bright red and warm and later returning to normal color In more severe cases recovery is less complete, slight cyanosis is constantly present and the part remains cooler than normal Color changes always affect the tip of the digit less often half or the whole digit they appear first in the tip and later in the more proximal portion Recovery follows the reverse order first the proximal portion and later the tip The usual order of color changes described by patients is first pallor, then cyanosis and lastly redness If an individual has been working with his hands at the onset of an attack a waxy pallor followed by cyanosis appears but if the hand is at rest at the level of the heart cyanosis appears first In the stage of pallor or cyanosis there is no blood flow through the capillaries due to spasm of the digital

tomy on individuals with normal vessels and on patients suffering from Raynaud's disease state "The fact that in Raynaud's disease the vessels are still abnormal after sympathectomy seems to provide conclusive evidence that the abnormality does not lie in the sympathetic nervous system" White[4] agrees with Lewis that total syncope of the digits indicates a local vascular fault, but favors Raynaud's original idea that, at the onset of the disease the recurrent attacks of symmetrical vasospasm are due to an abnormal activity of the vasoconstrictor nerves Hyndman and Wolkin[38] have confirmed the observations of Lewis that exposure to cold continues to cause color changes in affected digits after preganglionic or postganglionic sympathectomy They agree with Lewis that the vascular spasm in Raynaud's disease is a local phenomenon

From the above one may conclude that in severe cases of Raynaud's disease a local vascular hypersensitivity to cold is the inciting factor in the causation of the spasm of affected arteries While opinion as to the primary cause of spasm in mild cases remains divided, evidence is accumulating to support the conception of Lewis As exposure to cold is a constant factor in promoting attacks of arterial spasm in both mild and severe cases of Raynaud's disease, and other factors, such as an emotional stimulus like fear which raises the vasomotor tone, are inconstant, the writer favors the view expressed by Lewis and Pickering[39] that, in mild cases, closure of the arteries in attacks is due to two factors the abnormal local response of the affected vessels to cold and a normal increase of vasomotor tone For further discussion of the subject the reader is referred to the original articles

Definition A primary vasospastic type of functional disturbance of the digital arteries having a bilateral and symmetrical distribution The vascular spasm is intermittent and occurs on exposure to cold or cold and emotional stimuli The abnormal vascular response to cold is probably an inherited characteristic The condition usually occurs in young women and is characterized by recurring short attacks of waxy pallor or, less often, cyanosis of the digits induced by cold The affected parts become numb and their temperature falls to that of their environment In mild cases recovery from attacks is complete, the digits first become red and warmer and later become normal in color and temperature In advanced cases recovery is incomplete, cyanosis and coldness being present between attacks, sclerodermatous changes may develop in the skin resulting in fibrosis of the skin and subcutaneous tissue with gangrene of the digit

The disease is not common nor is it peculiar to any nationality Monro[40] and Brown[41] both found about one case occurring among 3 000 patients Brown estimates that 20 per cent of peripheral vascular disturbances belong to the functional group and that 44 per cent of vasospastic disturbances are of the Raynaud type

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arteries [6] Pulsation in arteries like the radial or dorsalis pedis may be smaller than normal but is always present With spontaneous recovery or after placing the hands in warm water the affected part becomes bright red and warmer from relaxation of the arteries, first in the proximal portion of the digit and gradually to the tip

Pathology No significant changes have been found in the sympathetic ganglia in Raynaud's disease In mild, uncomplicated cases, pulsation of the digital arteries is normal in volume and capillary pulsation is visible in the finger tips The texture of the skin is normal and no pathological changes abnormal for the age of the patient are demonstrable in the digital arteries [4] In severe cases, the digital arteries no longer dilate to the normal extent on warming the hands [3a] and capillary pulsation is markedly diminished or absent The affected digit may be slightly swollen or smaller than normal and taper at the tip from atrophy of the pulp The skin may be less mobile than normal, particularly in fingers showing atrophy, but is never hard and fixed as in acroscleroderma In such cases minute areas of superficial gangrene of the skin at the tips of the fingers are common, these heal slowly leaving pitted scars The digital arteries show varying degrees of intimal hyperplasia with or without thrombosis The intimal thickening would appear to be responsible for the incomplete dilation of digital arteries that are not thrombosed, but cannot be considered a cause of the attacks of discoloration or of the subsequent development of superficial necrosis of the skin for this intimal thickening is no greater than that found in many patients with warm hands [4] There is no evidence that the vasospasm responsible for the attacks of discoloration can cause gangrene Thrombosis of digital arteries or smaller arteries and capillaries in the tips of affected digits would appear to be essential for the development of gangrene

In certain cases presenting the Raynaud phenomenon, and particularly in those with incomplete recovery of the circulation between attacks of discoloration, sclerodermatous changes may be found in the skin and subcutaneous tissues of affected digits—sclerodactylia, or these changes may be more diffuse and involve the backs of the hands, arms, face, and neck—acroscleroderma or acrosclerosis, or in rare instances the lesions may become more generalized—diffuse or generalized scleroderma In the early stage of sclerodactylia the cold and discolored digits are slightly swollen, flexion is impaired, and the skin is smoother, less mobile, and hard Later the skin becomes tense, shiny and bound down to adjacent structures, the nails are deformed and thickened blisters and cracks may form over the knuckles or tips of the fingers, and whitlows are common

Minute areas of gangrene may develop on the fingertips, or the gangrene may extend to involve the end of the fingers so that amputation may be required Pain and stiffness of joints are present and arthritic changes in the phalangeal joints with atrophy of bone in the terminal phalanx are common findings

In the histological examination of cases of scleroderma Matsui[43] found thickening of the horny layer of the skin with atrophy of the malpighian layer and flattening of the papillae The corium was dense and poor in capillaries and cells and the sweat and sebaceous glands and the hair follicles were atrophic The digital arteries showed fibrosis of the media and intimal thickening, often causing almost complete occlusion of the lumen of the vessel Thrombosis in different stages or organization was not uncommon Round cell infiltration about the digital arteries and in the adjacent tissues often was present While the digits were more markedly affected Matsui found lesions of a similar character in the skin of the arms face and chest and in the muscles and internal organs

There has been much discussion as to whether the sclerodermatous changes in certain advanced cases of Raynaud s disease are the direct result of the primary vasospastic disturbance or are manifestations of a different disease Seller[44] expressed the opinion that Raynaud s phenomenon or syndrome is never present in diffuse scleroderma that sclerodactylia has its origin in scleroderma but that diffuse scleroderma and acrosclerosis are two different diseases O Leary and Waisman[45] agree with Seller that there is enough difference between the clinical manifestations of diffuse scleroderma and acrosclerosis to warrant the consideration of acrosclerosis as a separate clinical entity but they have found the histological characteristics of the skin lesions to be similar in the two conditions They believe that the pathogenesis of the sclerotic disturbance is similar in sclerodactylia and acrosclerosis and admit that acrosclerosis may be only a complication of Raynaud s disease The diffuseness of the sclerodermatous lesions found by Matsui in cases of sclerodactylia and acrosclerosis and subsequent clinical[46, 47, 48, 49] and pathological studies[4, 50, 1] on scleroderma by others strongly support the conclusion that sclerodactylia acrosclerosis and diffuse scleroderma are manifestations of the same disease and that scleroderma is not the direct result of the vasospastic disturbance in Raynaud s disease

The cause of scleroderma is unknown but it is now generally agreed that the disease primarily affects collagenous connective tissue[48b, 49, 5, 52] the essential changes consisting of edema induration and later fibrosis if the disease becomes chronic The collagenous connective tissue of the

body as a whole is affected but the clinical manifestations and the pathological changes may be more marked in one or more areas of the body such as exposed parts of the skin,[47] skeletal muscles,[4] or internal organs heart,[49] lung [5] gastro-intestinal tract,[3] and kidney [4] In sclerodactylia complicating Raynaud's disease, the clinical manifestations are swelling from edema immobility, and hardness of the skin from induration, and major nutritional changes and atrophy from fibrosis and the associated circulatory disturbances

As diffuse scleroderma tends to be progressive and run a more acute course than the more localized forms of scleroderma, it is not surprising that peripheral vascular disturbances are less marked in diffuse scleroderma than in acrosclerosis or sclerodactylia In fact, acute diffuse scleroderma may develop and prove fatal without discoloration of the acral parts and without evidence of any significant pathological changes in the vascular system [0] In cases of Raynaud's disease complicated by sclerodactylia, Prinzmetal [6] observed that the areas of greatest circulatory insufficiency coincide with the areas of greatest change in the skin and found, as did Lewis [3] that the affected digit is unable to maintain a normal skin temperature and that no rise in temperature is present after the injection of histamine He was able to demonstrate that if a normal finger was compressed by a rubber cot or adhesive tape the same temperature reaction occurred as in sclerodactylia From his carefully controlled studies he came to the conclusion that the tight, inelastic skin and subcutaneous tissues of the finger in sclerodactylia by constricting the blood vessels and diminishing blood flow, were responsible for the more severe clinical course of cases of Raynaud s disease complicated by this condition Prinzmetal considers the atrophy of the terminal phalanx in sclerodactylia as probably due to the tight skin

In addition to the mechanical effects of the tight, inelastic skin in sclerodactylia, sclerodermatous lesions of the digital arteries and arterioles must be considered an important factor contributing to the diminished blood flow and the development of major nutritional changes particularly gangrene Thrombosis of the digital arteries is a common finding in advanced cases of Raynaud s disease complicated by scleroderma[4] and probably is responsible for the more extensive ulceration and gangrene usually present

It seems clear that the primary vasospastic disturbances in Raynaud s disease cannot be the cause of the changes in the collagenous connective tissue in scleroderma, for these changes are not confined to the digits but develop in other areas of the body in the absence of vasospastic dis

turbances On the other hand it seems likely that the collagenous connective tissue changes in scleroderma are chiefly if not wholly responsible for the incomplete recovery of a digit from attacks of discoloration in cases of Raynaud s disease complicated by sclerodactylia and for the pain and major nutritional changes that develop following induration and fibrosis of the skin and underlying tissues from scleroderma

Symptoms As attacks of discoloration in Raynaud s phenomenon are provoked by cold the onset usually occurs in cold weather At first one finger or the end of a finger becomes white (local syncope) or blue (local asphyxia), but soon the bilateral and symmetrical distribution of the discoloration becomes manifest and one or more digits of both hands are affected Less often the toes may show similar changes The discoloration beginning at the tip of the finger tends to spread and involve a part or the whole of one or more digits on both hands The part feels numb and cold and an aching pain may be present Upon entering a warm room or placing the hand in warm water or rubbing the affected part, it becomes bright red and warm, tingles and may ache and throb After a few minutes the color and temperature return to normal until another attack occurs Sweating of the hands and feet not only during but between attacks is common In cold weather the patient may have one or more attacks each day but in warm weather they tend to disappear The frequency of attacks may remain unchanged for years more often they increase in frequency in cold weather and also occur in warm weather

An increase in the frequency and in the duration of attacks from a few minutes to an hour or more and their occurrence in warm weather as well as in cold are indications of increased severity and progression of the disease When recovery from an attack of discoloration is incomplete as evidenced by persistent slight cyanosis and coldness, structural changes are present in the artery of the affected digit and nutritional changes are prone to develop In a person with persistent cold hands an emotional disturbance or a painful stimulus may provoke an attack At this stage the finger may be slightly smaller than normal but the skin wrinkles and nutritional changes usually are limited to minute sores at the tip of the affected digit These sores are painful and slow to heal A deficient capillary circulation repeated minimal traumata and finally thrombosis of the capillaries would appear to be the cause of these minute areas of gangrene of the skin

In advanced cases of Raynaud s disease the affected digits may become stiff and painful flexion is impaired and the patient experiences difficulty

in doing fine work These manifestations mark the onset of scleroderma as a complication In the early stage the finger is swollen and the skin smooth and less mobile but it soon becomes firm, tense, and shiny Later the skin becomes bound down to underlying tissues and the finger shrinks and tapers at the end The nails become ridged, thickened, and deformed Whitlows are not uncommon and may result in the loss of a nail The distal phalanges become shortened from atrophy and absorption of bone Ulcers form at the end of the affected digit, gangrene develops and may necessitate amputation Thrombosis of the digital artery[4] is a common finding and probably is the cause of the more extensive ulceration and gangrene in cases of this type

Diagnosis The essentials in the diagnosis of primary Raynaud s phenomenon (Raynaud s disease) are (1) a history of intermittent but recurrent attacks of pallor or cyanosis of the digits, chiefly of the hands and less often of the feet, induced by exposure to cold, (2) a bilateral and symmetrical distribution of the discoloration, (3) pulsation in arteries proximal to the part affected, (4) absence of severe pain except in cases complicated by infection or scleroderma, (5) gangrene if present, limited to minute areas at the end of the finger and in most cases confined to the skin, unless scleroderma occurs as a complication when ulceration and gangrene may be more extensive Hunt[7] restricts the diagnosis of Raynaud s disease to cases in which nutritional changes, if present at all, are limited to the skin and excludes cases complicated by sclerodactylia However it is generally recognized that scleroderma may develop as a complication of Raynaud s disease and cause major nutritional disturbances with and without ulceration and gangrene of the affected digit

As already mentioned, intermittent attacks of cyanosis or pallor of the digits may occur in conditions such as thromboangiitis obliterans, cervical rib, scleroderma and injury to digits from vibrating tools Gangrene, often bilateral but usually asymmetrical, frequently occurs in thromboangiitis obliterans and arteriosclerosis of the extremities It is important therefore, to rule out conditions in which Raynaud's phenomenon may develop as a secondary manifestation and those in which gangrene may be due to primary organic vascular disease before making a final diagnosis of Raynaud s disease As the phenomenon may be an early but secondary manifestation of thromboangiitis obliterans and may appear before signs of primary scleroderma are recognized Allen and Brown[3] make one of the criteria in the diagnosis of Raynaud s disease a history of signs and symptoms of intermittent discoloration in

duced by cold for at least two years with nutritional changes in the digit if present limited to minimal grades of cutaneous gangrene

Course and Prognosis The history of attacks of discoloration indicates the rate of progress of the disease Patients may have short attacks of discoloration followed by complete recovery recurring in cold weather for many years without the development of nutritional disturbances When the attacks increase in frequency and duration and occur in warm as well as in cold weather the malady is gaining ground With the development of persistent color changes followed by nutritional changes in the digits more particularly scleroderma the progress is unfavorable, pain is often distressing and the condition becomes disabling

Treatment Stimuli from exposure to cold or cold and emotion are the precipitating factors in attacks of discoloration in Raynaud s disease Treatment must be directed towards preventing or lessening first the direct action of cold on the digits and second an increase in general vasomotor tone from the cooling of the body and from emotional stimuli Bathing in cold water exposure out of doors in windy cold weather and the handling of cold objects should be avoided Patients should be urged to keep not only the hands and feet but the body warm by the wearing of suitable clothing The hands should be kept under the bedclothes at night The importance of keeping the body as well as the extremities warm in peripheral vascular disturbances is not sufficiently appreciated A normal body weight should be maintained The avoidance of fatigue and emotional strain is important In mild cases with attacks occurring only in cold weather and followed by complete recovery this plan of treatment will lessen the frequency of attacks of discoloration and may prevent the progress of the disease When attacks occur in warm as well as in cold weather and increase in duration of the attacks is progressive and recovery incomplete no other form of medical treatment except residence in a warm climate which is seldom possible seems to affect the course of the disease

Tissue extracts are of no value Thyroid therapy has been recommended in patients with a low metabolic rate but it is of benefit only if hypothyroidism is present The initial increase in the basal metabolic rate and improvement in the peripheral circulation following the oral administration of thyroid hormone are not maintained by continuous thyroid therapy except in patients with hypothyroidism [9] Many vasodilator drugs have been used in the treatment of Raynaud s disease but none produces a sufficiently prolonged vasodilation to be effective and practical in the prevention and treatment of attacks of discoloration The

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scleroderma often show improvement. Unfortunately the late results of sympathectomy, especially in the upper extremities are often disappointing. After six months or a year or two attacks tend to recur. Factors contributing to the failure of sympathectomy to maintain the immediate postoperative peripheral vasodilation would appear to be (1) the recovery of intrinsic tone[64] and the development of an increased sensitivity to circulating adrenaline[6,] or other hormones[60] after sympathectomy (2) failure of the operation to remove the primary cause of the spasm—the local vascular fault of Lewis[3] (3) structural changes in and around the digital arteries which prevent a maximal dilatation,[4] (4) regeneration of sympathetic fibers[67] and function.

Within a few days of cervicothoracic ganglionectomy in cases of Raynaud's disease Lewis and Landis[33a] observed that the maximal vasodilation consequent on the release of constrictor tone was not maintained; the part became paler but remained warmer than before operation. This indicated a recovery of intrinsic vascular tone known to occur in animals after sympathectomy. They found that the hand did not become warmer on warming the body but the cutaneous vessels contracted or relaxed in response to local changes in temperature. After the sympathectomy they immersed one of the affected fingers in water at 15° C and were able to produce an attack of discoloration which supported the view of Lewis[3] that the vascular spasm of the digital arteries is due to local sensitivity to cold and not to abnormal vasomotor impulses. Lewis ascribed the improvement in the circulation of the fingers persisting after sympathectomy to removal by the operation of normal vasoconstrictor tone and attributed the better and more permanent results after lumbar ganglionectomy to the mildness of the affection in the feet as compared to the hands and to the fact that normal vasoconstrictor tone is much greater in the feet than in the hands.

More recently a number of observers have made a careful study of the circulatory changes in both normal and abnormal cutaneous vessels of the hands and feet following sympatetic denervation. Freeman[68] showed that the blood flow in a sympathectomized hand varies with the metabolic needs of the tissues and not with the body temperature. In view of the increased sensitivity to adrenaline developing in the blood vessels of animals after severance of the vasomotor nerves Freeman, Smithwick and White[6] tested the sensitivity to adrenaline of denervated arteries in the human and found that they became sensitive to physiological dilutions of adrenaline six to eight days after sympathectomy, the sensitivity being greater in the vessels of the hands than in those of the

nitrites, acetylcholine and nicotinic acid, chiefly affect vessels of the head and neck and like acetyl beta-methylcholine, cause no significant increase in the blood flow of the digits Ganglion-blocking drugs—tetraethylammonium chloride or bromide (T E A),[60a] hexamethonium (C_5 and C_6),[61] and the adrenolytic and sympatholytic drug Priscoline (2 benzyl 4-5 imidozaline hydrochloride)—have a peripheral vasodilating effect in the digits approximating that from reflex heating or paravertebral sympathetic block The administration of T E A or hexamethonium releases vasoconstrictor tone but, in doses adequate to produce an effective digital blood flow for the relief of attacks of discoloration, these drugs produce an increase in pulse rate and cardiac output and a fall in blood pressure The development of hypotension,[60b 61] especially in the upright position makes these drugs unsuitable for the treatment of Raynaud's disease Priscoline has a direct vasodilator action on the peripheral blood vessels[6 d] adequate for the control of attacks of discoloration[6 d e] without causing a significant general vasodilation and fall in blood pressure Side effects include flushing of the face, fainting, giddiness, palpitation, goose flesh, and, occasionally nausea and abdominal pain In beginning treatment with Priscoline Douthwaite and Finnigan[6 d] recommend an oral test dose of 25 milligrams If no untoward symptoms develop treatment by the drug is continued The oral administration of 150 to 00 milligrams of Priscoline a day, in divided doses of 25 to 50 milligrams has been found effective in lessening the frequency and severity of attacks of vasospasm in Raynaud's disease Although Priscoline would appear to be the safest effective peripheral vasodilator drug known the control of vasospastic attacks requires the daily administration of the drug This greatly limits the value of this method of treatment

Sympathetic denervation is the only known therapeutic procedure which may produce an adequate sustained improvement in the circulation of the affected digits Since Adson and Brown[63] in 1929, reported upon the favorable results of cervicothoracic ganglionectomy in Raynaud's disease the release of central vasoconstrictor tone by sympathetic denervation has proved to be the most effective means of producing a persistent vasodilation in the extremities, not only in vasospastic disturbances but also in organic arterial disease accompanied by increased vasoconstrictor tone The immediate results of sympathectomy in moderately advanced cases of Raynaud's disease are good the cold hands become warm and the skin dry, attacks of discoloration disappear, painful superficial ulcers heal more promptly and even digits affected by

Simmons and Sheehan[5] confirmed the observations of Freeman Smithwick and White[6] that the sensitivity to adrenaline is greater after postganglionic than preganglionic denervation but found that the hyper sensitivity to adrenaline which reaches its maximum in the first three weeks after both types of operation diminishes with time and may have disappeared when a clinical relapse of the Raynaud phenomenon in the hands occurs six months or longer after the operation In a search for other possible causes of the late relapses after sympathetic denervation of the arm they demonstrated reflex sweating of affected digits and a rise in skin temperature of the ulnar side of the hand after the injection of novocain in all patients having a late clinical relapse As these findings indicated the existence of sudomotor and vasoconstrictor fibers Simmons and Sheehan concluded that regeneration of vasoconstrictor fibers is the cause of the late relapses after sympathectomy

Barcroft and his associates [3] using the plethysmograph made measurements of the blood flow in normal cutaneous vessels of the hands and feet before and daily for one week after sympathectomy and later at longer intervals In the hands [3] the blood flow decreased to one quarter of the postoperative rate in a week and to one eighth in two weeks at the end of one to three months the blood flow was about the same as before operation The blood flow in the feet [3b] as in the hands decreased rapidly in the first week but unlike the hands remained at about twice the preoperative level in one to three months The surface skin temperature of the digits of the hands and feet at ordinary environmental temperature remained at or near the normal vasodilation level in spite of the decrease in blood flow with the recovery of vasconstrictor tone After six months the physiological effects of sympathectomy on normal and abnormal digital arteries appeared to be permanent in the feet but many sympathectomized hands responded to reflex vasodilation and showed evidence of sudomotor activity indicating regeneration of sympathetic fibers Thirty six hands denervated for frequent attacks of Raynaud s disease were tested one to six years after preganglionectomy [3, 4] Vaso motor and sudomotor reflexes had returned in many of the hands but 50 per cent had no recurrence of vasospastic attacks and 40 per cent had obtained significant relief in 10 per cent attacks persisted or recurred within six months after the operation These clinical results were in gen eral agreement with those of Robertson and Smithwick

It now seems clear that the failure of sympathectomy to maintain the immediate postoperative peripheral vasodilation of both normal and ab normal digits is due to the regain of tone of the cutaneous vessels which

feet On the eighth day following a cervicothoracic ganglionectomy for Raynaud's disease the injection of adrenaline was promptly followed by a fall in surface skin temperature and all the signs of vasospasm in the digits The sensitivity to adrenaline was greater in the denervated vessels of the hands than in those of the feet Hampel[69] found that sensitivity to adrenaline in denervated vessels reaches its maximum on the fifteenth or sixteenth day after sympathectomy and that the sensitivity is twice as great in postganglionectomy as in preganglionectomy After a cervicothoracic ganglionectomy, Telford[70] noted that the Horner syndrome remained in patients having a relapse of the Raynaud phenomenon in the hands As the stellate ganglionectomy is postganglionic for the arms and preganglionic for the eye, he concluded that section of preganglionic rather than postganglionic fibers might explain the more permanent effects of sympathetic denervation of the foot

These observations led Telford[70a] and Smithwick,[71a] working independently, to devise a preganglionic type of operation for denervation of the upper extremity by division of the white rami of the second and third dorsal ganglia and cutting the sympathetic trunk below the third dorsal ganglion It is now generally agreed that a preganglionic sympathectomy is more effective than a cervicothoracic ganglionectomy in relieving attacks of Raynaud's disease Telford[70b] found the immediate results uniformly good but the late results remain unsatisfactory Some years after the operation about 45 per cent of the patients remained well, 20 per cent had less frequent and less severe attacks the operation was considered a failure in 35 per cent Twenty-two patients incapacitated from Raynaud's disease remained well after lumbar ganglionectomy

Robertson and Smithwick[72] studied the vasoconstrictor activity of the affected digital vessels of the upper extremity after different types of sympathectomy They found that preganglionectomy or ganglionectomy eliminated vasoconstrictor activity in 80 per cent of extremities in the first year after operation, but 65 per cent of such extremities showed evidence of vasoconstrictor activity one to five years later, and 80 per cent after five years They attributed the recurrence of vasoconstrictor activity in the first year after operation to incomplete denervation, and its later appearance as probably due to nerve regeneration Even though the recurrence of vasoconstrictor activity was high one or more years after sympathetic denervation, the clinical results of preganglionectomy were classified as 'good' or 'fair in 85 per cent of patients five or more years after the operation After lumbar ganglionectomy the incidence of vasoconstrictor activity was lower and the clinical results were 'good' or 'fair in all lower extremities

may be increased by using copper constantan thermocouples connected to a sensitive galvanometer or by the portable Tycos dermatherm In vasospastic disorders digital vessels free of structural disease as in mild Raynaud's disease respond to reflex vasodilation like normal vessels If structural changes are present in the digital artery or major nutritional changes from scleroderma have developed as in advanced cases of Raynaud's disease, there may be little or no rise in skin temperature after maximum vasodilation and any rise is slow rather than prompt in developing and does not reach the normal vasodilation level If the skin temperature after maximum vasodilation is subtracted from the normal vasodilation level one has an indication of the part played by structural changes in and about the vessels in decreasing blood flow the obstruction index [8] If the surface skin temperature reaches 30° C (86° F) an immediate favorable response to sympathectomy may be expected but a maximum rise to 28° C (83° F) or less is an indication of serious structural disease in or about the digital arteries and little or no improvement in the circulation may result from a sympathectomy

In mild cases of Raynaud's disease sympathectomy is not indicated When attacks of discoloration increase in frequency and duration and occur at a higher temperature than formerly sympathectomy should be recommended The presence of nutritional changes in the skin—minute sores on the tips of affected digits tapering of the fingers—is an indication of structural changes in the digital vessels which may prevent maximum dilatation of these vessels If the surface skin temperature of the digits after reflex vasodilatation approaches the normal level sympathectomy may be expected to result in an appreciable benefit to the patient The late results of the operation are good in the feet in almost all patients but in the hands there is a recurrence of attacks of discoloration usually less severe than before operation in at least 15 per cent of patients due to nerve regeneration Fortunately regenerated fibers function poorly for the late clinical results are better than might be expected following the recurrence of vasoconstrictor activity [3d, 1] The better and more permanent results of sympathetic denervation in the feet than in the hands would appear to be due to the milder affection of the feet the greater vasodilation persisting after the operation the better protection of the feet from the direct effect of cold and the lesser tendency to nerve regeneration

In cases of Raynaud's disease complicated by scleroderma the affected digit is unable to maintain a normal cutaneous temperature After reflex vasodilatation it may show no rise in skin temperature or a gradual slight

occurs in the first three weeks after sympathetic denervation There is no completely satisfactory explanation for the regain in tone but it would appear to be due to changes in the intrinsic properties of the smooth muscle of the vessels[64] and to their increased sensitivity to circulating adrenaline[65] and possibly an unknown circulating hormone[66] As hypersensitivity to adrenaline diminishes with time and may disappear[67] with regained tone persisting changes in the intrinsic properties of smooth muscle of the vessels following sympathectomy would seem to be the more important factor Relief and then a recurrence of the Raynaud phenomenon in the first six months after sympathectomy is an indication of incomplete sympathectomy In the next six to twelve months after sympathectomy the blood flow in normal digits is maintained at a little above the preoperative level, the surface skin temperature at or near the normal vasodilation level The digital arteries no longer constrict in response to body cooling[69] or emotional stimuli if denervation has been complete They constrict from the direct effect of cold but can be protected by the wearing of suitable clothing on the hands and feet in cold weather and by avoiding washing in cold water These physiological effects of sympathectomy are more or less permanent in the feet, but many hands after six months or a year, show evidence of regeneration of vasoconstrictor fibers in spite of precautions taken at operation to prevent its occurrence An appreciation of these early and late effects of sympathetic denervation on the circulation of the digits is of importance in the selection of patients for sympathectomy and in the assessment of the results of operation

Before recommending sympathectomy for the relief or amelioration of peripheral vascular disturbances it is desirable to determine by a preoperative test the maximal vasodilation that may be expected from the operation by the intravenous injection of foreign protein (typhoid vaccine),[4] peripheral nerve block by procaine[3] [75] [6] spinal anesthesia for the lower limbs[77] [78] [9] paravertebral injection,[80] warming the body in a cabinet,[13] or the immersion of one of more limbs in water at 43° to 45 C[14] Immersion of an extremity is the simplest and most practical method for clinical use The results are more reliable than from warming the body[81] but paravertebral injection or spinal anesthesia for the lower limbs possibly gives more accurate results For details of these methods the reader is referred to the original reports When maximum vasodilation is induced under controlled conditions the surface skin temperature of a normal digit rises promptly to a minimum of 31° C and a maximum of 36° C the normal vasodilation level The surface skin temperature

may be increased by using copper constantan thermocouples connected to a sensitive galvanometer or by the portable Tycos dermatherm In vasospastic disorders, digital vessels free of structural disease, as in mild Raynaud s disease, respond to reflex vasodilation like normal vessels If structural changes are present in the digital artery or major nutritional changes from scleroderma have developed as in advanced cases of Raynaud s disease, there may be little or no rise in skin temperature after maximum vasodilation and any rise is slow rather than prompt in developing and does not reach the normal vasodilation level If the skin temperature after maximum vasodilation is subtracted from the normal vasodilation level one has an indication of the part played by structural changes in and about the vessels in decreasing blood flow the obstruction index[78] If the surface skin temperature reaches 30° C (86 F) an immediate favorable response to sympathectomy may be expected but a maximum rise to 28° C (83° F) or less is an indication of serious structural disease in or about the digital arteries and little or no improvement in the circulation may result from a sympathectomy

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In cases of Raynaud s disease complicated by scleroderma the affected digit is unable to maintain a normal cutaneous temperature After reflex vasodilatation it may show no rise in skin temperature or a gradual slight

rise far below the normal vasodilatation level In most instances sympathectomy results in no improvement In the less severe cases sympathectomy or the administration of ACTH or cortisone may be followed by some softening of the skin healing of ulcers, and the relief of pain and stiffness of the digits but the sclerodermatous process tends to progress with a recurrence of symptoms Gask and Ross[30] report complete failure from sympathectomy in eight out of eleven cases In advanced scleroderma the immediate results of the operation are disappointing and amputation of affected digits may be necessary

Secondary Raynaud's Phenomenon Secondary Raynaud's phenomenon occurs in primary obliterative vascular disease and will be referred to later in discussing thromboangiitis obliterans and arteriosclerosis Reference will be made now to other conditions in which intermittent or continuous discoloration of the digits may develop and must be differentiated from Raynaud's disease

Traumatic Raynaud's Phenomenon Raynaud's phenomenon may develop in riveters stonecutters, and other workers with *vibrating tools* such as pneumatic hammers[8] or pounding machines After these tools have been used for a few months or longer intermittent attacks of numbness and pallor develop on exposure to cold, in one or more digits of the hand using the tool or machine Unless the hand is exposed to cold the attacks do not come on while the patient is at work Recovery from an attack is complete and may be accelerated by rubbing or gentle warming of the hand It would seem that rapid vibrations render the digits sensitive to cold Nutritional changes in the affected digits are rare but the sensitivity to cold tends to be persistent even after a change of occupation If the condition becomes troublesome a change of occupation and the treatment outlined for mild cases of Raynaud's disease are indicated

Sensitivity of the fingers to cold and the Raynaud phenomenon in male patients may follow a *local injury* In Lewis and Pickering's case[39] the Raynaud phenomenon developed on exposure to cold in the right ring finger some months after injury with a fives ball and in Hunt's case[37] twenty-eight years after incision and drainage of a whitlow Richards[63] describes a case in which attacks of blueness and pallor on exposure to cold occurred six months after recovery from an injury with infection of the right index finger and later spread to the thumb and middle finger and tip of the ring finger A patient seen by the writer developed coldness and pallor on exposure to cold of the two distal phalanges of the right index finger and the left index and middle fingers following injuries received while playing baseball

Occasionally patients with a *rib anomaly*—cervical rib, rudimentary first rib or a normal first rib with muscular atonia and a drooping shoulder—the so called scalenus anticus syndrome—may complain of spasmodic attacks of numbness and pallor of the fingers or persistent blueness and coldness of one hand In certain cases nutritional changes in the nails small ulcers which are slow to heal or gangrene of the tip of a terminal phalanx or of a whole finger may develop If the onset has been characterized by aching pain in the arm with weakness and wasting of muscles indicating injury to the brachial plexus causing a brachial neuritis the development of persistent blueness and coldness of the hand likely is due to disuse [84] Raynaud s phenomenon with or without nutritional changes in the digits would appear to result from an interference with blood flow through the subclavian artery from rib pressure In these cases the subclavian artery may appear normal show an aneurysmal dilatation or its lumen may be partially occluded by thrombosis or by compression from fibrous tissue [9]

In the earlier stages of the condition a normal pulsation of the palpable arteries of the arm is present but may be interrupted temporarily by certain movements of the head the shoulder or the arm as from carrying a weight in the hand or on the shoulder After varying periods of intermittent compression of the subclavian artery between clavicle and rib attacks of numbness and pallor on exposure to cold or cyanosis and coldness of the hands develop Later pulsation in the radial, ulnar or brachial arteries and even in the subclavian may be decreased or absent Occasionally a pulsatile swelling in the neck with a bruit due to an aneurysmal dilatation of the subclavian artery is an early symptom When ulceration or gangrene of the tip of one or more digits is present it is an evidence of complete obstruction of the vessel supplying the necrosed area

It seems evident that no one factor is responsible for the development of peripheral vascular symptoms in rib anomalies As they usually develop in adult life and only a small percentage (12 per cent)[85] of those with a rib anomaly have symptoms severe enough to require surgical treatment the anomaly alone does not seem to provide an adequate explanation for the vascular disturbances Todd[86] suggested that the changes in the arteries of the arm are trophic in character and caused by paralysis of the sympathetic fibers from pressure on the lowest trunk of the brachial plexus The absence of similar vascular disturbances following cervicothoracic ganglionectomy in individuals with normal ves

sels would seem to exclude paralysis of sympathetic fibers as a cause From observations on cases of cervical rib with no evidence of obstruction of the subclavian artery but with organic obstruction of the brachial artery or more distal arteries of the arm, Telford and Stopford[87] expressed the opinion that irritation of the sympathetic constrictor fibers of the first dorsal nerve root from stretching or pressure was the primary cause of the changes in the arteries of the arm distal to the axillary They suggested that prolonged constriction of the larger arteries must constrict or even obliterate the vasa vasorum and thereby cause nutritional changes in the walls of the arteries, which would lead ultimately to thrombosis of these arteries As preganglionic sympathectomy without section of the first dorsal root results in a fairly complete sympathetic denervation of the upper extremity it is unlikely that irritation of the lowest trunk of the brachial plexus can be the cause of the vascular symptoms in cases of cervical rib

It has long been known that removal of a cervical rib will relieve the vascular and nerve symptoms present More recently Adson and Coffey[88] found that dividing the tendonous attachment of the scalenus anticus muscle, without resection of the cervical rib, would relieve symptoms and they have stressed the role of this muscle in the production of vascular and nerve symptoms in patients with normal first ribs and in cases of cervical rib Their observations have been confirmed by others[89, 90] and the term scalenus anticus syndrome' now is frequently applied to the group having a normal first rib but manifesting rib pressure symptoms Adson found symptoms more common in women than in men The higher incidence in women has been attributed to greater drooping of the shoulder girdle coupled with general debility and muscular atonia

Temporary obliteration of the pulse related to certain movements of the head or arm no doubt results from temporary compression of the subclavian artery between clavicle and rib, but it fails to explain the cause of persistent partial or complete obliteration of the pulse in distal arteries or of major nutritional changes resulting in ulceration and gangrene of the fingers These findings have been shown to result from organic changes in vessels supplying the necrosed area In cases of this type organic changes in and around the subclavian artery are not uncommon These may consist of an aneurysmal dilatation of the third part of the subclavian with or without thrombosis and fibrous tissue around the artery binding it to the underlying rib Lewis and Pickering[30] and Eden[91] attribute these changes to trauma of the subclavian artery from repeated

compression between the rib and clavicle, and the complete obliteration of the pulse in brachial, ulnar, radial, or more distal arteries they attribute to emboli dislodged from a thrombosis in the subclavian artery

From a study of cases with rib pressure syndromes Walshe, Jackson, and Wyburn Mason[9] concluded that vascular symptoms were not due to irritation or paralysis of sympathetic fibers but to mechanical interference with blood flow through the subclavian artery They differentiate three syndromes of vascular disorders (1) recurrent coldness cyanosis pallor, and tingling of the hands and digits associated with the transient obliteration of an otherwise normal radial pulse by placing the arms in certain positions, (2) the syndrome of patent aneurysmal dilatation of the third part of the subclavian artery, which may include components of the first syndrome and in addition increased pulsation and bruit with or without thrill over the subclavian artery above the clavicle (3) the syndrome of a partly or completely occluded aneurysmal dilatation of the third part of the subclavian artery consisting of signs of ischemia in the upper limb and sometimes of embolism in the digits leading to small regions of gangrene They found as have others that no one factor—cervical rib rudimentary first rib scalenus anticus muscle, or drooping shoulder girdle—operating alone is the causation of the mechanical interference with the blood flow in the upper extremity

As structural changes in and around the subclavian artery usually are found with rib anomalies and very rarely with a normal first rib, these anomalies not only contribute to the compression of the subclavian artery by weight bearing or by clavicle and rib with certain movements of the arm and cause transient color changes in the hands but would appear to be chiefly responsible for the structural changes that may develop and result in aneurysmal dilatation and local thrombosis of the subclavian artery which may be followed by the dislodgement of emboli and permanent obliteration of the pulse in more distal arteries In rib anomalies with vascular symptoms the posterior border of the scalenus anticus muscle has been found to produce an indentation on the subclavian artery Symptoms may be increased by tension on this muscle and division of its tendonous attachment is followed by a partial or in some cases complete relief of vascular symptoms not due to permanent obliteration of the pulse in distal arteries Vascular symptoms with a normal first rib are found most commonly in women with a drooping shoulder girdle and general muscular atonia These two factors probably play a more important role than the scalenus anticus muscle in the production of attacks of blueness and coldness of the hands

Diagnosis Rib anomalies may be bilateral but pressure effects are nearly always unilateral Raynaud's phenomenon occurring in one hand excludes Raynaud's disease The temporary obliteration of the pulse by certain movements of the shoulder or arm and by weight bearing or a combination of vascular and nerve symptoms in one extremity are indications of rib pressure as a cause of the symptoms The presence or absence of an abnormal first rib may be determined by an X-ray examination

Treatment After symptoms from rib pressure have developed, the condition tends to be progressive Prolonged rest may relieve attacks of blueness and coldness and mild sensory and motor disturbances, but if symptoms persist or gangrene of a digit develops, surgical intervention is indicated

Traumatic Arterial Spasm In certain cases a blow on the finger[39] or a crushing injury of the digits may be followed, after recovery from the initial damage by the development of Raynaud's phenomenon localized to the injured digits The attacks of discoloration occur on exposure to cold but usually are absent in warm weather and tend to disappear gradually after a few months This vasospastic disturbance of small arteries is not common but may occur after both minor and major injuries It may be a latent manifestation of hypersensitivity to cold incited by trauma

Trauma to tissues adjacent to *larger arteries,* as the femoral or brachial by gunshot wounds fractures, dislocations, contusions, crushing injuries or at operation may cause spasm of a segment of the artery followed by continuous pallor or cyanosis with coldness of the distal part of the extremity Pulsations in arteries distal to the trauma are absent or very weak The clinical manifestations are similar to those in acute arterial occlusion but pain is usually absent Raynaud's phenomenon is not present When the area of trauma has been exposed by operation the segment of artery in spasm may show no evidence of injury or thrombosis In cases of this type pulsations return in a few hours pallor or cyanosis disappears, and the distal part becomes warm indicating that spasm was the cause of the absent pulsations discoloration and coldness Less often acute muscle necrosis (Volkmann's contracture) or gangrene may result Bywaters and Belsey[83] found intense arterial spasm the common cause of ischemic necrosis of muscles in the crushing injuries of air raid casualties Griffiths[84] and Cohen[9] consider blockage by thrombus or damage to collaterals important factors in the development of muscle necrosis or

gangrene in the condition called traumatic segmentary artery spasm[9r] or traumatic arterial spasm[9]

The inciting cause of the spasm evidently is trauma but there has been no general agreement as to the mechanism by which trauma causes spasm of a large artery Leriche[7] suggested irritation of the periarterial nerve plexus by the trauma and recommended treatment of the condition by a local sympathectomy (periarterial stripping) or arteriectomy Cohen[8] considered rapid stretching by the trauma of the smooth muscle of the artery the effective stimulus Kinmonth and Simone[89] observed that the local arterial spasm might persist for hours after the operation of periarterial stripping Kinmonth[10] has shown that mechanical trauma of a large artery—pinching longitudinal stretching handling with forceps or rubbing with gauze—may cause a long lasting spasm that can not be relieved by sympathectomy In rabbits he studied the effect of smooth muscle relaxing drugs on spasm of the femoral artery produced by mechanical trauma He found that the intravenous injection of papaverine copper citrate procaine and priscol failed to relieve the spasm but that the local application of these drugs was effective in relaxing the spasm The most effective drug was papaverine The application of a warm 2 5 per cent solution of papaverine sulphate produced in a few minutes a permanent relaxation of the spastic artery In two patients with arterial spasm local treatment with papaverine caused permanent relaxation He has suggested that traumatic arterial spasm is due to mechanical stimulation of the vessel wall resulting in sustained contraction

Treatment The immediate therapy of cases of traumatic arterial spasm will depend on the general condition of the patient and the cause of the mechanical trauma After appropriate treatment of shock hemorrhage and dehydration and of fractures dislocations or crushing injuries the area of arterial trauma should be explored and the artery examined for direct injury, compression by a hematoma or thrombosis proximal or distal to the local spasm The artery should then be covered by a warm 2 5 per cent solution of papaverine sulphate If spasm is not relieved in ten to fifteen minutes Kinmonth[90] recommends closing the wound loosely and leaving a fine polythene tube for the installation at intervals of 1 per cent papaverine until the circulation is restored Contusion of an artery or thrombosis may require an arteriectomy Muscle ischemia and necrosis from arterial spasm may follow the splinting of a limb If damage of an artery is suspected in a fracture case Cohen[87] states that plaster should not be used and recommends a Thomas splint In crushing injury cases McMichael[1] suggested the application of a

tourniquet to the proximal part of the limb before the weight is taken off and then the gradual release of the circulation in hospital to prevent the sudden flooding of the circulation with toxic products from dead or dying muscle He also suggested the cooling of the injured limb with ice bags to decrease the rate of tissue autolysis If patients are treated before the death of muscle fibers occurs, Cohen believes that cooling the injured limb until the circulation returns increases the chances of muscle survival and may arrest muscle autolysis and renal sequelae

Atypical Raynaud's Phenomenon Blueness, coldness, less often pallor and numbness of the fingers toes, ears, or tip of the nose on exposure to cold may occur in association with two or more of the following signs and symptoms sensitivity to cold paroxysmal hemoglobinuria, hemolytic anemia urticaria purpura, and gangrene Cold is the usual precipitating factor for the development of the signs and symptoms The blueness and coldness of the digits may be spasmodic but more often are persistent and not the result of spasm of the digital arteries The associated clinical manifestations are not characteristic of Raynaud's disease The common causes of the color changes in the skin and the associated signs and symptoms are cold, autohemolysis, cold agglutinins, and cold precipitable proteins in the blood Both sexes are affected Similar acral changes not related to exposure to cold may be present in a rare disorder called essential thrombocythemia'

Syphilitic Cold Paroxysmal Hemoglobinuria In 1904 Donath and Landsteiner[100] described the mechanism of paroxysmal hemoglobinuria They showed that it was due to an autohemolysin absorbed by the erythrocytes in the cold, with lysis of the sensitized cells at a higher temperature if complement is present This type of hemoglobinuria occurs in certain cases of congenital or acquired syphilis The attacks occur on exposure to cold, and the onset is characterized by shivering malaise, and aches and pains followed by the passing of dark red urine In the prodromal stage the fingers, toes, ears or tip of the nose may become cyanosed or blanched and wheals in the skin may develop Harris *et al* [101] showed that the urticaria was due to a dermolysin which united with the skin at low temperature and that the whealing followed after rewarming of the skin The clinical manifestations in this type of hemoglobinuria would appear to result from the release of hemoglobin in the blood

Cold Hemagglutination In 1903 Landsteiner[10] described the phenomenon of cold hemagglutination agglutination of erythrocytes by a serum agglutinin in the cold but not at body temperature Clough and Richter[103] studied the cold agglutinins in a case of bronchopneumonia and

found that the serum agglutinated not only the patient's erythrocytes but all human erythrocytes at 22° C and below (not above 22 C) if the temperature was gradually lowered from 37° C If the erythrocytes were agglutinated first at low temperature the agglutination persisted to 27° C Shooter[104] found cold hemagglutinins active at 19° to 23° C in 0 9 per cent of presumably healthy individuals They are seldom present in dilutions greater than one in sixteen

Cold hemagglutination at high titers 1—1 8 or above at 0° C have been found in patients presenting the Raynaud phenomenon and a chronic hemolytic anemia with or without hemoglobinuria Attacks of cyanosis or pallor and numbness of fingers toes ears and nose closely resembling the Raynaud phenomenon are described The color changes in the skin would appear to be due to the clumping of the erythrocytes in the minute cutaneous vessels on exposure to cold and the return of normal color in the skin to the dispersal of the clumped erythrocytes in a warm environment Iwai and Mei Sai[10] described clumping of the erythrocytes in the capillaries of the cooled conjunctiva and suggested cold hemagglutination as the cause of the Raynaud phenomenon Others have confirmed their findings Stats and Wassermann[106] irrigated the conjunctiva with iced isotonic saline solution and using a binocular corneal microscope, observed intra vitam agglutinaton of the erythrocytes which broke up at an environmental temperature of 2° C Ferriman et al [107] used a slit lamp to investigate the effect of cooling and warming the conjunctivae On cooling the erythrocytes collected in clumps with stretches of clear plasma intervening At first the columns of erythrocytes and plasma moved slowly but with further cooling complete arrest occurred On warming the flow was resumed at first spasmodically and then quite abruptly the clumps disappeared and flow was restored Stats and Bullowa[108] have reported a case of cold hemagglutination with Raynaud's phenomenon and paroxysmal hemoglobinuria in which a symmetrical gangrene of the tips of fingers and toes followed prolonged exposure to moderate cold Good pulsations were present in the arteries of the upper and lower extremities The gangrene of the digits would appear to be due to thrombosis of the smaller digital arteries secondary to prolonged cessation of blood flow from clumping of the erythrocytes In cases of cold hemagglutination urticaria is absent and the Wassermann test is negative

Cryoglobulinemia In 1933 Wintrobe and Buell[109] reported a case of multiple myeloma in which an abnormal blood protein precipitated on

tourniquet to the proximal part of the limb before the weight is taken off and then the gradual release of the circulation in hospital to prevent the sudden flooding of the circulation with toxic products from dead or dying muscle He also suggested the cooling of the injured limb with ice-bags to decrease the rate of tissue autolysis If patients are treated before the death of muscle fibers occurs, Cohen believes that cooling the injured limb until the circulation returns increases the chances of muscle survival and may arrest muscle autolysis and renal sequelae

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ating in dry gangrene developed in the second left toe while the patient was in bed in hospital The application of ice to the skin produced an urticarial reaction Following the intravenous administration of ACTH there was prompt relief of the malaise chills and fever and control of the hemorrhagic manifestations but there was no significant alteration in the cryoglobulin fraction of the gamma globulin Signs and symptoms returned in twenty four hours after discontinuing the treatment Oral cortisone 100 milligrams daily, was ineffective Intramuscular Duracton therapy controlled the constitutional and hemorrhagic manifestations for a time but gradually became less effective The patient died in an attack of bronchopneumonia and pulmonary edema A biopsy of a purpuric area of skin confirmed the findings of Lerner and Watson[110] On histological examination of the digital arteries of a gangrenous toe there was no evidence that the gelifying of the cryoglobulin had affected the intima of the thrombosed arteries The complete obstruction of the artery resulting in gangrene was due to thrombosis secondary to the spontaneous precipitation of the cryoglobulin

The chief clinical manifestations of cryoglobulinemia are an urticarial reaction of the skin induced by cold, anaphylactoid purpura—usually widespread—affecting skin and mucous membrane and an atypical Raynaud phenomenon As suggested by Barr[111] it seems clear that the obstruction of blood flow in the minute vessels of the skin and mucous membranes resulting from the enmeshing of erythrocytes by the precipitated cryoglobulin plays a dominant role in the production of the spasmodic and more persistent color changes in the skin and the hemorrhagic manifestations in skin and mucous membranes But the urticarial reaction to cold is an important contributing factor in the development of the purpuric state in skin There is no proof that the gelification of the cryoglobulin in the circulation is directly responsible for the increased permeability of the minute vessels with the effusion of erythrocytes and plasma Superficial ulceration of a purpuric spot is an indication of complete obstruction of minute vessels which may be due to the precipitated cryoglobulin Gangrene of a digit is due to complete obstruction of an artery from a fibrin thrombus secondary to gelification of the cryoglobulin

Essential Thrombocythemia (Essential Thrombocytosis, Essential Thrombophilia) In 1930 Epstein and Kretz[113] reported a case of increased platelets in the circulating blood admitted to hospital because of recurrent excess bleeding from mucous membranes The patient gave a history of an impending gangrene of the second right toe in 1917

withdrawal of blood from the body Blueness of fingers, toes, rims of the ears, and tip of the nose and mottling of the arms and legs on exposure to cold were present Later attacks of coldness and blanching of the digits and tongue developed Lerner and Watson,[110] in 1947, discovered a similar protein in a patient with urticaria and widespread purpura on exposure to cold A biopsy of the skin showed a moderate round celled infiltration about the capillaries in the purpuric areas They proposed the term cryoglobulin to represent a group of proteins having the common property of precipitating or gelifying from cooled serum and if present in high concentration of precipitating spontaneously at room temperature In two cases of cryoglobulinemia studied by Barr *et al*,[111] one patient had attacks of urticaria, purpuric spots resembling Henoch's purpura on the upper and lower extremities, and bleeding from nose and gums on exposure to cold, the other patient had multiple myeloma and complained of easy fatigue in winter weather pallor, numbness and pain in his fingertips and toes and mottled blanching of the ears and face on exposure to cold Later, he had frequent bleeding from nose and gums and hematuria The blood flow in the minute vessels of the conjunctiva was studied with a biomicroscope following the application of a tube of iced water to the eyeball They observed considerable aggregation of the erythrocytes slowing of the circulation, segmentation of columns of blood and in some areas reversal of flow The changes in blood flow were evident for several minutes after the withdrawal of the cold stimulus In a case of essential cryoglobulinemia investigated by Volpe *et al*[11] and observed by the writer, the patient first noticed purplish red tender spots on his ears on exposure to cold, which disappeared in about two weeks After several years larger purplish spots appeared on the hips and legs and their appearance was preceded by chilliness, a definite rigor and fever The larger purpuric spots usually bled and ulcerated, healing occurred after several weeks, leaving areas of mottled brown pigmentation or circular depressed scars Later the patient complained of cyanosis numbness and tingling of the fingers and toes on exposure to cold, deafness, attacks of crampy abdominal pain with diarrhea and tarry stools and frequent epistaxis a hemorrhagic stomatitis and pharyngitis developed A month before admission to hospital his right great toe became blue cold, and painful within a few minutes but normal color returned in about five days with rest in bed warmth to the foot, and oral priscoline Two weeks later a similar change occurred in the left great toe but failed to improve and a dry gangrene developed Similar color changes termin

is of the opinion that the administration of radioactive phosphorus (P_{32}) has a favorable effect

(For a more complete discussion of hemoglobinuria and purpura the reader is referred to Oxford Medicine volume II pages 779 and 8 3

Acrocyanosis Acrocyanosis (Nothnagel) or chronic acro asphyxia (Cassirer) is a term applied to a condition in which the hands from a little above the wrists to the fingertips are a persistent blue or blue red color are cold and clammy, and sweat profusely The feet may be affected Acrocyanosis like chilblain is found most commonly among young women living in a cold damp climate The condition is uncommon in cold, dry climates Cassirer[117] considered the vascular disturbance to be of vasomotor origin but Lewis and Landis[118] have shown it to be due to increased tone of the arterioles of the skin which is not quickly relieved by anesthetizing the nerves to the hand The increased tone of the arterioles would appear to be due to a local hypersensitivity to cold The capillaries are dilated and the persistent cyanosis is due to loss of tone of the minute vessels of the skin from the diminished blood flow and the continued low temperature of the hands The local injection of histamine causes the part to become red and warming the body produces a maximum dilatation of the arteries and arterioles of the hand There is no evidence of structural disease of the arteries and nutritional changes are absent in the skin and nails Acrocyanosis differs from Raynaud s disease in that the coldness and discoloration do not develop in attacks but are continuous and more diffuse

Treatment The condition seldom causes any serious disability and treatment consists in avoiding exposure to cold and wearing suitable clothing to keep the body and extremities warm Sympathectomy will relieve the condition but the severity of the disability is seldom if ever great enough to require operation

Erythema Pernio (Chilblain) Erythema pernio or chilblain develops after prolonged exposure to damp cold but not to frost, and appears as a raised rounded red swelling hot tender and itching on the fingers and dorsum of the hand on the toes and less often on the ears and tip of the nose In severe cases bullae may form The itching is constant and becomes more marked on returning from a cold to a warm environment Chilblain like acrocyanosis occurs most commonly in young women living in a cold damp climate Barber[119] has described two types of patient predisposed to chilblain one fat and phlegmatic with harsh dry skin on the legs the other a thin nervous type susceptible to infections and both having a tendency to bluish cold extremities

attributed to frostbite with a good recovery In 1931, the second and third right toes were amputated on account of dry gangrene Microscopic examination of the arteries showed sclerosis with obliteration of the lumen of the vessels A constant increase in platelets and recurrent hemorrhages were present until the death of the patient in 193 At postmortem examination the spleen was found to be atrophied and the bone marrow showed hyperplasia with an excess of megakaryocytes Epstein and Goedel[114] considered the condition a definite clinical entity and, in view of the persistent thrombocytosis and a hyperfunction of the bone marrow and recurrent hemorrhages, gave it the name of 'hemorrhagic thrombocythaemia

In 1937, Nygaard and Brown[11] reported five cases of recurring thrombosis of the large and small arteries and veins of the extremities and less often of the renal cerebral and coronary arteries They stated that the episodes of thrombosis may subside after a few hours or a few days with complete recovery, or the occlusions may lead to gangrene and subsequent amputation of a small or large part of the extremity In their cases recurrent hemorrhages were not a clinical feature Microscopic examination of occluded arteries from amputations showed a bland non organized type of thrombosis with a normal intima or slight cellular reaction in the wall of the vessel Of patients with occlusive lesions of the small arteries of the fingers and toes, one had a platelet count of over two million and two others had normal counts They considered this thrombosing condition a definite disease entity probably due to a loss of suspension stability of the platelets, and gave it the name essential thrombophilia'

In a group of eleven patients with an excessive number of platelets and hyperplasia of the megakaryocytes in the bone marrow studied by Wightman,[116] some of the patients had episodes of thrombosis of the small arteries of the fingers and toes in association with hemorrhagic manifestations

Platelet thrombi would appear to be the cause of the vascular disturbances present in the thrombosing condition described as essential thrombocythemia essential thrombocytosis or essential thrombophilia the manifestations depending on the size and site of the vessels occluded The vascular manifestations and their clinical course simulate those found in cryoglobinemia but cold is not a precipitating factor As spontaneous remissions and relapses occur in the course of the condition it is difficult to assess the effect of any special form of therapy Wightman

deeper than in erythrocyanosis and that the early lesions rarely disappear in warm weather

Treatment In the early stages of erythrocyanosis, warm clothing on the body and legs at the onset of cold weather and the avoidance of prolonged exposure to cold will usually prevent a recurrence In more severe cases rest in bed in a warm environment until the acute condition subsides is indicated If ulcers fail to heal after a period of conservative treatment, Telford recommends lumbar sympathectomy and reports a complete cure in two thirds of cases Allen *et al*[173] state that sympathectomy does not prevent recurrence of lesions after prolonged exposure to severe cold

Trench Foot and Immersion Foot Trench foot and immersion foot are terms applied to a condition which develops in the extremities usually the lower after prolonged exposure to moist cold A description of the condition among soldiers in the Napoleonic Russian Campaign of 181 was given by Larrey [174] and in World War I by Grattan [175] In World War II the condition occurred in soldiers shipwrecked sailors and Air Force personnel forced to bale out over the sea and has been described by different observers Under the title Trench Foot Knight[176] described in the British Medical Journal cases among civilians spending nights in a sitting position without moving in air raid shelters

After exposure to cold and wet for many hours or days the tissues are not frozen but the immersed limbs feel numb and powerless tender to touch but not painful or itchy boots feel tight from swelling of the feet the color of the skin becomes pale or waxy white with scattered cyanotic areas Ungley and Blackwood[177] describe the signs and symptoms in the affected limbs as passing through three stages prehyperemic hyperemic and post hyperemic

In the prehyperemic stage the affected limbs are cold numb discolored swollen and painless but tender to pressure sweating is absent movement of ankle and toes is impaired a stocking anesthesia is present If the patient attempts to walk he is unsteady and has the sensation of walking on air

In the hyperemic stage which develops in two to twenty four hours after removal from cold and wet the cold greyish limbs become reddish blue and hot to the touch (30° to 35 C – 86 to 95° F) [83] with the body covered and the limbs exposed to room temperature (0° C – 68 F) they become a deep purplish red on hanging down and blanch rapidly on elevation except in areas of threatened superficial gangrene Swelling increases and petechial hemorrhages and blisters containing straw-

Lewis[10b] has shown that prolonged exposure of the skin to cold at 9° C (48° F), in a predisposed subject, causes a chilblain lesion, but not in a normal subject. The skin lesions are characterized by dilatation of minute vessels, extravasation of erythrocytes and perivascular infiltration of lymphocytes and neutrophilic leucocytes, edema, and subacute or chronic inflammation of the skin and subcutaneous tissue. In mild cases, chilblain is present in cold damp weather and subsides in warm weather. In long standing cases fissures and cracks in the skin may develop and it becomes more susceptible to exposure to cold.

Treatment. Prevention is the best treatment of chilblain. In cold weather the body should be kept warm by the wearing of suitable clothing. Out of doors the patient should wear warm mitts and avoid prolonged exposure to cold.

Erythrocyanosis. Erythrocyanosis is a chilblain phenomenon affecting the lower half of the leg in young women. The condition begins in cold weather as a bluish discoloration and slight swelling of the posterior and lateral aspects of the lower half of the leg above the malleolus, which in early attacks disappears in warm weather to recur the following winter. After two or three winters the diffuse discoloration deepens and slightly raised purplish itchy painful patches appear, accompanied by increased thickening of the leg above the ankle. These painful nodules tend to break down leaving a round indurated ulcer one to two centimeters in diameter. The ulcers, which are more numerous near the ankle, slowly heal in a warm environment leaving depressed pigmented scars. According to Telford,[11] the histological changes in the nodules consist of cellular infiltration of subcutaneous fat, necrosis of fat, foreign body giant cells, and finally fibrosis. The general character of the histological changes in vessels, skin, and subcutaneous tissue in erythrocyanosis is similar but more marked than in chilblain. The lesions are due to the same cause, prolonged exposure to cold in a susceptible subject. According to Lewis[10] the manner of exposure determines the different location of the lesions in erythrocyanosis. He states that the condition came in with short skirts and thin stockings and will go out with them.

Erythrocyanosis closely simulates erythema induratum (Bazin's disease). Telford[11] considers the histological changes identical in the two conditions and questions the tuberculous nature of Bazin's disease. Montgomery *et al*[3] found a specific histopathological picture of tuberculosis present in 70 per cent of cases of erythema induratum. They point out that the lesions in this disease usually begin in the calf rather than above the ankle, that induration is more marked, that the ulcerative lesions are

but results from increased permeability of the capillaries The protein content of the edema fluid was found to be approximately 3 per cent indicating the presence of an inflammatory edema These findings in man are in agreement with those of Lorrain Smith et al [1 3] in experimental trench foot in rabbits On histological examination of tissues at the end of the exposure they observed swelling of the vessel walls but no thrombosis and an outpouring of fluid into the tissues containing fibrin and cells—an inflammatory reaction

In view of the intense vasodilatation that develops in immersion foot on warming the body it is evident that the minute cutaneous vessels are viable except in areas where necrosis may develop Lewis and Love[13] have shown that although there is marked vasoconstriction of the smallest arteries and strong arterioles during immersion in wet cold the blood flow in the minute vessels is not interrupted and is adequate to meet the metabolic needs of the tissues at the low temperature They have also shown that the redness of the skin which is known to develop after a hand has been exposed to ice cold water is due to dilatation of the minute vessels of the skin associated with an extremely slow blood flow and a greater diminution or absence of oxygen exchange It seems clear that that the low metabolic requirement of the tissues during exposure limits the damage to the tissues caused by the exposure to wet cold

The transition from the prehyperemic to the hyperemic stage occurs when the warming of the body releases the vasoconstriction of the arterioles and arteriovenous anastomoses in the acral parts of the affected limbs As the tone of the minute vessels is lessened (their walls damaged from exposure to cold and a vasconstrictor paralysis present as evidenced by absence of sweating), the increased blood flow following warming of the body results in an excessive vasodilatation of the minute vessels (skin temperature 31° to 35° C or 87° to 95 F)[83] increased edema, and the development of burning pain and tenderness of the skin The occurrence of burning pain and tenderness with a vasoconstrictor paralysis supports the idea of Lewis[131] that the red painful part is due to the inflammatory reaction resulting from injury to the skin Swelling petechial hemorrhages and blisters may be present on admisssion to hospital but more often appear first after the development of hyperemia Lorrain Smith et al [179] showed that rapid warming of parts exposed to wet cold increased edema and the intensity of the inflammatory reaction in the tissues Clinical experience has confirmed their observations Webster et al [13] observed and others have confirmed that cooling of the extremities during recovery from exposure relieved burning pain and rapidly

colored or blood stained fluid may appear on the foot, diminished or absent pulsations return in the peripheral arteries in the first twenty four hours Sweating is absent indicating a vasomotor paralysis A severe, constant burning pain develops in the foot, usually reaching maximum severity in twenty-four to thirty-six hours It is of the kind found in erythralgia is increased by warmth relieved by cooling, and increased by friction exercise and a dependent position of the limb In a week or ten days a shooting stabbing pain probably related to the return of function in efferent sympathetic fibers, begins in the dorsum of the foot and radiates to the toes Burning pain may be increased in intensity In a moderately severe case the hyperemic stage lasts for six to ten weeks If the limbs are not warmed but kept cool, sensory loss which may extend to the knees recedes in the first twenty four hours to the mid-foot, leaving an area of marked hyperalgesia In a few days the area of anhydrosis recedes and corresponds with the area of sensory loss to cotton wool touch, swelling subsides in three to four weeks The skin of blackened insensitive areas peels off leaving a superficial ulcer which heals very slowly Thrombosis of larger arteries is rare and amputation for gangrene is seldom necessary Weakness and, later wasting of the muscles of the foot with diminished electrical excitability are present and recovery is slow

The post hyperemic stage lasts for weeks and months The chief complaints are sensitivity of the affected acral parts to cold and minor trauma pain excess sweating and swelling after exercise

Wet cold is the essential factor in the causation of the trench or immersion foot syndrome Immobility dependency, and constriction of the circulation in the limbs by wearing apparel are contributing factors According to Lewis[10a, b] the first change in prolonged exposure to cold is a generalized vasoconstriction of all surface vessels—arteries, arterioles minute vessels or capillaries, and veins—to safeguard against an excessive fall of body temperature As thermoregulation is an important function of the acral parts (see page 501), vasoconstriction is more intense and the injurious effects of cold on the tissues greatest in the distal portion of the limbs If the skin temperature falls to 10° C (50° F) or lower for a time, the part becomes numb and touch and pain sense are lost, muscles are weakened Exposure of a normal hand in water at 5° C (41° F) for a short period as three hours results in definite swelling, as evidenced by a 15 per cent increase in volume of the part[18] The edema which affects both skin and subcutaneous tissue is not due to imbibition of water by the skin for it develops in a hand covered by a rubber glove,

of function When the patient is convalescent and able to walk he must take the same precautions as patients with chronic obliterative vascular disease (see page 506 (64))

In the post hyperemic stage the affected limbs tend to become cooler than normal limbs in the same environmental temperature The majority of patients have a good recovery of function but in others the damaged tissues may remain sensitive to cold and trauma and burning pain and tenderness persist With the recovery or regeneration of sympathetic fibers there is excessive sweating and an increased vasoconstrictor tone If slowly healing open lesions of the skin are present treatment by warming of the body or reflex vasodilation by warming an unaffected hand and arm in a box heated by electric light bulbs to increase blood flow should be tried The pain associated with the residual inflammatory changes in the tissues is similar to that present in minor causalgia and may be due to activation of sensory fibers by efferent sympathetic impulses If pain is a troublesome symptom lumbar sympathectomy should be considered for its relief

Frostbite is a condition in which freezing of tissue occurs from exposure to dry cold The areas commonly affected are the fingers ears nose cheeks and toes Wind favors the development of frostbite Tight coverings on the legs and feet and immobility increase the danger of frostbite of the toes Lewis[129] states that the freezing point of skin is close to —1 C but due to the property called supercooling[130] it does not freeze unless the surface temperature is—5 C (23 F) or even —0 C (—4 F) Brahdy[128] found frostbite frequent at —10 to —13 C (14 to 8 F), and rare even with high wind at —4 4 C (24° F)

Freezing and its after effects may vary from redness and slight swelling to blistering with or without extravasation of blood and greater swelling to necrosis of tissue The after effects depend on the severity duration, and depth of the freezing and the subsequent reaction of the tissues during thawing The first and mildest manifestation of frostbite is a stinging or pricking sensation in the white area of frozen skin During thawing a red flare appears around the frozen area and gradually invades it the surrounding red flare fades leaving the frozen area red slightly swollen and itchy the skin is tender to friction and painful—first degree frostbite If the freezing is more intense whealing is followed by blistering with or without the extravasation of blood greater swelling and burning pain rather than itching—second degree frostbite If cold is intense it may result in a superficial gangrene of the skin The surrounding red flare (due to arteriolar dilatation and dependent

decreased the edema and that too early removal of cooling was followed by a marked increase in edema, the extravasation of blood, and a spread of gangrene The increase in severity of signs and symptoms early in the hyperemic stage and their subsidence on cooling of the extremity would seem to indicate that increased tissue requirement for oxygen at the higher temperature was the cause After rescue and warming the body, areas of skin usually in the toes, may remain cold These areas of threatened gangrene are an indication of complete arrest of blood flow in the minute vessels supplying the affected part Kreyberg[133] believes that stasis in the minute vessels is the cause of the complete obstruction resulting in superficial gangrene As an inflammatory edema is present stasis and secondary thrombisis would seem to be the more likely cause

In the prevention of trench foot, warm clothing for the body, clean feet frequent changes of woolen socks and properly fitting waterproof boots are the essentials Prolonged standing in wet cold without exercise should be avoided The same measures should be adopted for the prevention of immersion foot with the addition of waterproof covering for the body as a protection from wet, cold, and wind Sitting in a cramped postion with the limbs dependent for long periods and the wearing of any apparel constricting the limbs should be avoided

Patients should be transferred to hospital on a stretcher and not allowed to stand or walk Care should be taken to avoid trauma in the removal of wet clothing and boots and in the preliminary cleansing of the limbs The body should be covered with warm blankets, with the limbs elevated above heart level and exposed at a room temperature of 21° C (70° F) The patient should be given a warm drink, to release general vasoconstriction and appropriate treatment of his general condition Cooling of the limbs early in the hyperemic stage is most important The limbs may be cooled by dry ice-bags,[137] cooling cabinets[134, 13, 136] or an electric fan[13, 17] Ungley[13] found that prolonged cooling at a skin temperature of 21° C (70° F) caused discomfort and recommended that the skin temperature be not reduced below 23° C (73° F) Burning pain would appear to be reduced at toe skin temperature of 23° to 26 C (73° to 79° F) The control of burning pain is an indication of the efficiency of the cooling and if it can be controlled by an electric fan it is the simplest method Later pain may be relieved by exposure of the limbs at room temperature Rest in bed must be continued until superficial skin lesions heal, the inflammatory reaction in skin and subcutaneous tissue subsides and there is satisfactory recovery

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a part of the ischemic area. If the wall of the affected minute vessel was necrotic one would expect hemorrhage rather than obstruction of blood flow. Gangrene of the deeper tissues results from complete obstruction of small arteries by a true thrombus.

Treatment. Frostbite is preventable under most circumstances if due precautions are taken. A warm body is most important for the prevention of cooling of the hands and feet. In extreme cold with wind the body should be kept warm by the wearing of loose clothing in many layers with an outer covering of windproof material. Silk gloves and warm mittens in a wind and water proof gauntlet should be worn on the hands and two pairs of soft woolen socks and well fitting pliable water proof boots or an Eskimo mukluk type of boot on the feet. The ears should be covered. If a stinging sensation is felt or a white patch appears on the exposed face it should be warmed immediately with the uncovered hand. The skin should be kept dry. Lewis and Love[146] have shown that supercooling displays itself in greater degree in dry skin and that the application of oil to the feet discourages freezing. Adequate oxygen in high altitude frostbite is important.[147] Individuals with chronic obliterative vascular disease of the extremities or a general disability from any cause should avoid exposure to extreme cold. A part once frozen is more susceptible to frostbite and extra care must be taken to prevent a second attack.

The treatment of frostbite depends on the severity, duration and local circumstances of the exposure. If a white patch develops on the exposed face and is promptly covered by a warm hand there is usually complete recovery. If the hands or feet become numb they should be uncovered and placed under the clothes—the hands near the body of the patient and feet near that of a companion. The frozen tissues are brittle and should not be damaged further by rubbing. If the hands and feet remain numb or if exposure with numbness has been prolonged the patient should be removed on a stretcher and placed at rest in a warmer environment. The body should be wrapped in blankets and the patient given a hot drink to relieve generalized vasoconstriction; the limbs should be left exposed and rewarmed gradually. The application of heat in any form greater than body heat to the frozen part increases the damage to frozen tissues during thawing[140, 143] and must be avoided. After a gradual restoration of circulation in the affected parts they should be gently cleaned with soap and cool water and wrapped in sterile dressings with pressure areas protected. Limbs should be elevated above heart level to decrease edema. In high altitude frostbite oxygen should be adminis-

upon a local axon reflex), the local dilatation of minute vessels in the frozen area and the local wheahng and blistering compose the 'triple response' of Lewis which Lewis and Love[130] have shown to result from the release of an H substance in the skin from injuries to the skin cells by ice crystals

If freezing is more prolonged, penetration is deeper affecting both skin and subcutaneous tissue The first stinging sensation of freezing is followed by numbness the skin is waxy white and the frozen part solid and fixed When a part is frozen solid and freezing ceases to extend there is probably no further damage to the tissues until thawing begins[138] The end result is necrosis—third degree frostbite Following thawing, blisters form with or without the extravasation of blood causing separation of the superficial layers of skin which ultimately dry and peel off leaving healed skin, otherwise blistering is absent and the tissues are darker in color The frozen part ultimately becomes black dry, and mummified From the results of the Indian ink injections of Rotnes and Kreyberg[139] and the intravenous injections of fluorescein of Lange and Boyd[140] in experimental frostbite, it is evident that complete obstruction of blood flow in cutaneous vessels, resulting in necrosis develops after the initial redness and swelling in the frozen part If injections are made shortly after thawing begins, Indian ink or fluorescein is visible in the minute vessels, but it is not visible after injections made twenty-four hours later At this stage they found the minute vessels dilated and packed with erythrocytes which Kreyberg attributes to the escape of plasma from the damaged capillaries leaving the erythrocytes stranded—the phenomenon of stasis Greene[141] states that clumping of the erythrocytes is not found in viable tissues and he and Kreyberg[133] are of the opinion that stasis without true thrombus formation can cause necrosis of tissue It seems clear that clumping or conglutination of erythrocytes filling the minute cutaneous vessels precedes a complete obstruction of blood flow through these vessels, but it is not equally certain that this alone can cause necrosis, for conglutination in frostbite has been shown to be a reversible process by Brown and Landis[14] The obstruction in the minute vessels would appear to become an irreversible process causing complete obstruction resulting in superficial gangrene after the erythrocytes break down and fuse forming hyaline thrombi Kreyberg[133] agrees that these 'thrombi are composed of broken down blood cells after stasis but considers the breakdown of erythrocytes as paralleling the necrosis in other tissue elements He states 'They are not causing necrosis but they are suffering necrosis as

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tered If open lesions are present, penicillin should be administered intramuscularly to prevent or control infection Later, treatment should be similar to that of chronic occlusive arterial disease of the extremities (see page 506 (64))

Posttraumatic Painful Disorders of the Extremities In 1900, Sudeck[144] called attention to a condition characterized by persistent severe pain stiffness, and osteoporosis following fractures trauma to joints and sprains He considered the syndrome a reflex atrophy of bone and it has been referred to as Sudeck's atrophy ' Later Leriche[97] observed that injury to the nerve plexuses in the adventitia of arteries or even mild trauma to joints particularly in the region of the wrist or ankle may be followed in a few days by persistent pain, vasomotor disturbances, and osteoporosis In the early stage after the onset of pain he observed increased local heat and vasodilatation and often swelling later vasoconstriction usually developed, the extremity became cool clammy, and cyanosed in the dependent position, and the skin became thin, smooth and shiny Osteoporosis of bones in the region of the trauma developed in three or four weeks after the injury This has been attributed to the loss of calcium due to the hyperemia present Leriche and Fontaine[14] believe the pain and associated disturbances result from abnormal vasomotor reflexes and have described the condition under the term 'posttraumatic painful osteoporosis They found that periarterial sympathectomy often was followed by relief of the persistent severe pain and a striking improvement in other symptoms Fontaine and Herrmann[146] recommend periarterial sympathectomy for painful lesions in the wrists and ankles and ganglionectomy for injuries affecting more proximal joints Others have called the condition 'posttraumatic osteodystrophy '[147] reflex dystrophy of the extremities '[148] posttraumatic dystrophy [149] 'traumatic vasospasm '[150] and posttraumatic pain syndrome [151] and have confirmed the finding of Leriche and his associates that sympathectomy usually is effective in relieving the persistent pain and other clinical manifestations with the exception of osteoporosis Recalcification has been found to be a slow process and seldom is complete

A similar but more severe syndrome has long been known to develop following trauma causing partial destruction of a peripheral nerve, and occurring most frequently after wounds of the median or sciatic nerves As burning pain is the first and major complaint, Weir Mitchell[1] called the condition 'causalgia In this syndrome the chief clinical manifestations are constant burning pain and hyperalgesia in the distal cutaneous

area to which fibers of the injured nerve are distributed Pain and tenderness develop during the stage of healing of the wound The pain is aggravated by light touch movement warmth dependency of the affected part and emotional stimuli It is relieved or lessened by cooling The skin of the digits is red and warm thin smooth shiny and hairless and often wet with sweat Osteoporosis is present Immediate and often permanent relief of pain has been obtained from sympathectomy

The similarity in the history and clinical findings in cases of post traumatic painful osteoporosis and causalgia is striking Homans[133] has reported cases of the former under the name minor causalgia a hyperesthetic neurovascular syndrome

In the past decade special attention has been called to a painful disability of the shoulder and hand which may develop at the onset of or days and weeks following a cardiac infarction[14,15] A similar syndrome has been reported in cases of cervical osteoarthritis[16] periarthritis of the shoulder or without a known cause[13] It is commonly referred to as 'the shoulder hand syndrome In cases with cardiac infarction pain varying in severity develops in one or both shoulders and is usually followed in a few days by stiffness pain and swelling of one or both hands The fingers may be tender pinker and warmer than normal or a violet red color and cooler than normal After weeks or months the swelling subsides and there is a shrinkage of the subcutaneous tissue and muscles of the hands and fingers but no ulceration or gangrene Skin changes simulating sclerodactylia have been reported[11] In this late stage osteoporosis is present and many patients develop a Dupuytren s contracture usually of the ring finger Thickening and shortening of the palmar fascia would appear to be a rare finding in cases of posttraumatic painful osteoporosis and median nerve causalgia but the other clinical manifestations are of the same general character in the three conditions and suggest a common underlying mechanism in their production

Many theories have been advanced to explain the cause of the pain and the associated vasomotor and nutritional disturbances in these painful disorders of the extremities They are commonly referred to as reflex sympathetic disorders While it is true that early sympathectomy usually gives permanent relief from the pain there is no satisfactory evidence that sympathetic fibers convey pain impulses or that these impulses reach the spinal cord by way of the sympathetic ganglia It is generally agreed that painful stimuli both from somatic structures and viscera are mediated only by somatic nerves and conveyed in fibers that have their cell stations in the posterior root ganglia

Irritation of a peripheral nerve or arterial nerve plexus caused by direct injury, inflammatory reactions in adjacent tissue, or scars left in the healing process would appear to be the one essential factor for the development of pain and the associated vascular and nutritional disturbances in the cutaneous distribution of the affected nerve. It has long been known that stimulation of the distal end of a cut posterior root causes a long-lasting vasodilatation in the area of skin innervated by the cut nerve. This has been called antidromic vasodilatation,[158] and has been shown to result from the release of a histamine-like substance in the skin.[159] Miller and de Takats[149] have demonstrated increased blood flow in the affected part in the early stages after injury. Foerster[160] records that itching and burning pain in the skin are associated with the vasodilatation from stimulation of the distal ends of the posterior roots and of cutaneous nerves in man. Lewis[161] has produced the hyperalgesia characteristic of the causalgic state by direct mechanical injury of the skin and by electrical stimulation of a cutaneous nerve trunk or a branch of a cutaneous nerve. The same effects were obtained in patients subjected to ganglionectomy, indicating that sympathetic nerves are not essential for the production of hyperalgesia. If the skin was rendered anesthetic and then injured, no hyperalgesia developed until after sensation returned, indicating that injury to the skin and not the pain of the injury is responsible for the hyperalgesia. He found that if a cutaneous nerve trunk was blocked first by novocain proximal to the point of faradic stimulation, hyperalgesia did not develop in the distal cutaneous distribution of the nerve until the anesthetic effect had gone, but if the nerve was blocked distal to the point of stimulation, no hyperalgesia developed. These experimental findings confirm the observations of Tinel[16] that section of a damaged nerve distal to the lesion relieves burning pain but section proximal to it fails to give relief. From these observations it seems evident that nerve impulses conducted by fibers in the posterior root system subserving cutaneous sensitivity play an essential role in the development of the hyperalgesia characteristic of the causalgic state.

Lewis[163] states "There is much evidence to support the idea that all symptoms of causalgia arise at the periphery in response to changes caused there by cetrifugal impulses." He has drawn attention to the fundamental similarity of erythralgia (see page 506 (47)) and causalgic states and expressed the view that the tenderness, heat and redness in both conditions are due to the release in the skin of a pain-producing substance. According to Lewis, the change in the skin is mediated by a special sys-

tem of nerves which he has called nocifensor nerves In a critical review of cutaneous sensitivity Walshe[164] doubts the necessity of postulating the existence of a special set of cutaneous nerves He considers the system of nerve fibers in question as that belonging to the system of sensory nerves subserving cutaneous pain

Homans[1 3] is of the opinion that the hyperesthetic atrophic and sometimes edematous states present in minor causalgia may arise from irritation of a peripheral artery by pressure or by minor infection or by irritation of nerves about a large sized artery or a multitude of small vessels in a limb He believes that the mechanism of hyperalgesia described by Lewis is adapted to setting up and maintaining the causalgic state but does not offer a satisfactory explanation for relief of pain by sympathetic block He has suggested that afferent impulses arising from sensory nerve endings in the blood vessels enter the spinal cord via the posterior roots and make reflex arcs with outgoing sympathetic fibers and that reflex impulses are responsible for the causalgic state

Livingstone[1 1b] divides posttraumatic pains into three groups (1) causalgia ( ) minor causalgia and (3) posttraumatic pain syndromes He considers the signs and symptoms in the three groups manifestations of sensory nerve irritation and thinks that probably all have a similar underlying disordered physiology According to Livingstone afferent impulses from a focus of irritation in a peripheral sensory nerve acting on the internuncial pool of neurons in the spinal cord serve to disturb its normal functioning The central perturbation of function involves the sympathetic nerves and the somatic motor nerves and the peripheral effects brought about by the motor activity of each initiate afferent impulses which add themselves to those from the focus of irritation to sustain and augment the central activity

Doupe *et al*[16] describe two types of posttraumatic pain in injuries of the peripheral nerves one a paroxysmal or distal causalgic pain the other a dystrophic pain They observed that causalgic pain was directly related to the alternating activity of the sympathetic sudomotor and vasoconstrictor fibers that occurs in the thermoregulation of body temperature emotional excitement fear of noise a deep breath or pin prick stimuli known to aggravate causalgic pain They found that reflex vasodilation did not abolish causalgic pain and concluded that the relief obtained after sympathectomy was due to the interruption of efferent sympathetic impulses and not to the resulting vasodilation and increased blood flow removing a pain producing substance as suggested by Lewis They used peripheral nerve block to determine if the burning pain

Irritation of a peripheral nerve or arterial nerve plexus caused by direct injury inflammatory reactions in adjacent tissue, or scars left in the healing process would appear to be the one essential factor for the development of pain and the associated vascular and nutritional disturbances in the cutaneous distribution of the affected nerve It has long been known that stimulation of the distal end of a cut posterior root causes a long-lasting vasodilatation in the area of skin innervated by the cut nerve This has been called antidromic vasodilatation,[1 9] and has been shown to result from the release of a histamine-like substance in the skin [1 9] Miller and de Takats[159] have demonstrated increased blood flow in the affected part in the early stages after injury Foerster[160] records that itching and burning pain in the skin are associated with the vasodilatation from stimulation of the distal ends of the posterior roots and of cutaneous nerves in man Lewis[161] has produced the hyperalgesia characteristic of the causalgic state by direct mechanical injury of the skin and by electrical stimulation of a cutaneous nerve trunk or a branch of a cutaneous nerve The same effects were obtained in patients subjected to ganglionectomy indicating that sympathetic nerves are not essential for the production of hyperalgesia If the skin was rendered anesthetic and then injured, no hyperalgesia developed until after sensation returned, indicating that injury to the skin and not the pain of the injury is responsible for the hyperalgesia He found that if a cutaneous nerve trunk was blocked first by novocain proximal to the point of faradic stimulation hyperalgesia did not develop in the distal cutaneous distribution of the nerve until the anesthetic effect had gone, but if the nerve was blocked distal to the point of stimulation, no hyperalgesia developed These experimental findings confirm the observations of Tinel[16] that section of a damaged nerve distal to the lesion relieves burning pain but section proximal to it fails to give relief From these observations it seems evident that nerve impulses conducted by fibers in the posterior root system subserving cutaneous sensitivity play an essential role in the development of the hyperalgesia characteristic of the causalgic state

Lewis[163] states There is much evidence to support the idea that all symptoms of causalgia arise at the periphery in response to changes caused there by cetrifugal impulses ' He has drawn attention to the fundamental similarity of erythralgia (see page 506 (47)) and causalgic states and expressed the view that the tenderness heat, and redness in both conditions are due to the release in the skin of a pain-producing substance According to Lewis the change in the skin is mediated by a special sys

pulses play a dominant role in the causation of causalgic pain by the cross stimulation of afferent sensory fibers that nerve impulses from fibers of the injured nerve subserving cutaneous pain release pain producing substances which render the tissues in the cutaneous distribution of the injured nerve unduly sensitive to pain and are the cause of the early vasodilation tenderness and sensitivity of the skin that sympathetic nerves are not essential for the development of hyperalgesia but that efferent sympathetic impulses cause exacerbation of causalgic pain by the activation of sensory fibers The relief of pain and the cure of the causalgic state at least in its early stages support the conclusion that efferent sympathetic impulses play a dominant role in maintaining the causalgic state

Doupe *et al*, Nathan and Echlin *et al*[109] believe that pain is the central feature in the causalgic state and that the associated vasomotor disturbances—smooth glossy skin atrophy of pulp of the digits and the mottled osteoporosis of the small bones—are for the most part non specific They point out that these manifestations may occur in peripheral nerve lesions without causalgic pain In the early stage of an irritative peripheral nerve lesion the skin in the distal distribution of the injured nerve is red tender and warmer than the contralateral part due to antidromal or axonal vasodilation A low grade inflammatory reaction is present in the skin and subcutaneous tissue The mottled osteoporosis of small bones which appears a month or more after the onset of pain has been attributed to hyperemia of the affected bones With long continued pain the affected parts tend to become cyanosed and cooler than normal the joints fixed and the skin thin smooth and glossy Atrophy of the pulp of the digits and curving of the nails develop and osteoporosis becomes diffuse and loses its mottled appearance Disuse of the part from immobilization and fixation of joints resulting in a decreased cutaneous blood flow would appear to be the cause of the cooler cyanosed skin the atrophic changes and the diffuse osteoporosis It no doubt contributes to the development of a thin smooth skin but the disappearance of these skin changes in five days after section and freshening of the ends of a damaged ulnar nerve as observed by Head and Sherren[110] indicates that the irritative nerve lesion is the important factor in their development

Diagnosis If one realizes that injuries to median and sciatic nerves blood vessels and periarticular tissues particularly of the wrist and ankle may be followed in a week or more by the development of a constant severe pain and tenderness and later by the appearance of

originated at the site of the nerve lesion or near the termination of the nerve fibers. Peripheral nerve block relieved the distal but not the proximal pain. They have proposed the theory that causalgic pain in peripheral nerve lesions is caused by cross stimulation of the afferent sensory fibers by efferent impulses in the sympathetic fibers at the site of the nerve injury or in some cases at the nerve endings of the affected nerve. In the distal type of causalgic pain, they suggested that local tissue changes—edema, ischemia, or some other factor, determined by the injury to the limb as opposed to a primary injury of the nerve trunk—might be the cause of cross stimulation of the sympathetic and sensory fibers at their termination and give rise to pain. Nathan[166] considers this theory of Doupe and his associates equally applicable to causalgic pain occurring in partial and complete nerve lesions and also to cases of causalgia in amputation stumps, but is of the opinion that the pain impulses arise in the central end of the damaged nerve and not in the region which is felt to be painful. In support of the theory of Doupe *et al*, Katz and Schmitt[167] have demonstrated cross excitation between two nerve fibers in the crab. In experiments in cats, Granit *et al*[168] have shown that the cut region of a sciatic nerve serves as an 'artificial synapse.' Nerve impulses set up in a motor root are transmitted to the sensory fibers in a cut region of the nerve and can be picked up in the sensory root of the same segment. The effect was greatest in a freshly damaged nerve. They have shown that this fiber interaction also takes place at a crushed region of a nerve or a region subjected to moderate mechanical pressure.

Doupe *et al*[16] describe dystrophic pain as a persistent aching pain lacking the burning quality of causalgic pain and not affected by emotional stress or loud noises, but made worse by dependency and movement of the painful part, and worse at night. Local tissue changes consist of moderate edema, vasomotor changes, and a mottled osteoporosis as found by others in conditions described as Sudeck's atrophy, post-traumatic painful osteoporosis, reflex dystrophy of the extremities, minor causalgia, or posttraumatic pain syndrome. They make the tentative suggestion that dystrophic pain is secondary to nutritional changes resulting from disuse, deficient arterial supply, or deficient venous or lymphatic drainage.

It seems evident that the pain in major and minor causalgic states arises from irritation of a peripheral nerve at the site of injury or in some cases in its peripheral distribution, that efferent sympathetic im-

local blood flow and favors the development of stiffness of joints On account of the pain and tenderness patients limit voluntary movement of the extremity and many cannot tolerate massage, manipulation of joints or the application of heat The most effective measures for the relief of pain are paravertebral sympathetic block by procaine and sympathectomy

In the early stage of persistent pain the local injection of procaine to painful joints as recommended by Leriche[115] or at trigger points for pain as advocated by Livingstone[1 96] gives temporary and often permanent relief of pain Injection of a trigger point or paravertebral sympathetic nerve block depending on the site of the injury and the origin of the pain gives similar results in more severe cases If the relief of pain following one or more injections is of short duration a preganglionectomy should be recommended Relief of pain may be expected in most cases Sympathectomy usually is followed by a marked improvement in the stiffness of joints and the nutrition of the skin The absence of pain makes possible the treatment of any residual stiffness of joints or contractures by appropriate physical therapeutic measures Osteoporosis requires no special form of therapy

Graham *et al*[171] treated seventeen cases of shoulder hand syndrome with cortisone or ACTH and report relief of pain in about half the patients and complete recovery of function in three The relief of pain would appear to be due to the beneficial effects of hormone therapy on tissues at the irritative focus causing the pain

Erythralgia (Lewis)—Erythromelalgia (Weir Mitchell) In 187 Weir Mitchell[17] described a rare form of painful affection of the feet and in 1878[1 3] reported five additional cases of the same malady as a rare vasomotor neurosis of the extremities He named the condition erythromelalgia signifying a painful red extremity The chief clinical characteristics of the condition described were (1) attacks of burning pain in the foot or in both feet brought on first by prolonged physical exertion from walking and later also from standing warm bedclothes or firm pressure (2) pain relieved or arrested by the horizontal position or by cold (3) in the erect posture the affected parts flushed slowly in mild cases and almost at once in more severe cases the veins stood out the arteries throbbed for a time and the foot was first red later a dark purplish tint (4) the flushing which at first seemed to be an active condition was accompanied by a rise in temperature in a few minutes it became passive the arteries ceased to throb the heat lessened and

local nutritional changes in the skin and bones, diagnosis is not a difficult problem In lesions of the median and sciatic nerves, a history of injury or local infection followed by constant burning pain and tenderness in the distal distribution of the affected nerve suggests the diagnosis Obstruction by thrombosis of an artery proximal to the wrist or ankle is the usual finding in arterial lesions causing persistent burning pain and tenderness in fingers or toes Arterial pulsation is absent distal to the obstruction and proximal to the site of pain Rarely, a more distal vascular lesion—a glomus tumor of the digit—may be a cause of persistent pain and tenderness[148]

The development of persistent pain, tenderness, and stiffness of joints after an apparent recovery from a minor injury, such as a sprain of wrist or ankle should suggest the onset of a posttraumatic pain syndrome

If a similar symptom complex of pain and tenderness develops in one or both hands, preceded by pain in the shoulder, with no history of injury cardiac infarction should be suspected as the underlying cause

Course Symptoms in these painful disorders of the extremities vary more in degree than in kind and their severity and duration bear no definite relationship to the severity of the injury causing them In milder cases symptoms may subside in a few weeks without any special form of treatment or they may persist for months The persistence of pain after minor injuries to wrist or ankle would appear to be more common among workmen entitled to compensation To avoid the development of a traumatic neurosis an early diagnosis of the origin of the pain and the institution of appropriate treatment is of special importance Echlin *et al*[179] found that major causalgia occurred in about 20 per cent of war injuries of peripheral nerves, and state that the majority of patients show gradual spontaneous improvement but that the condition may persist over months or years They stress the importance of early treatment to prevent the development of progressive and irreversible changes in the affected tissues and perhaps even in the emotional stability of the patient In more severe cases a spontaneous recovery may occur after many months leaving a residual stiffness of joints but usually the causalgic state progresses if pain is not relieved The general physical and mental condition of the patient deteriorates and nutritional changes in skin and muscles accompanied by contractures and stiffness of joints progress in severity

Treatment The relief of pain should be the first consideration in treatment Prolonged rest of an extremity is not indicated, for it lessens

the skin and by deep pressure or increased tension from venous engorgement as was found in the burning pain produced by direct injury to the skin in normal individuals He showed that the critical temperature for the induction of pain was lower if the affected part was in a dependent rather than a horizontal position and that the pain was relieved, without a change in temperature by a return of the limb from the dependent to the horizontal position These observations support the view that burning pain is not entirely dependent upon the temperature of the affected part as suggested by Smith and Allen [177] but that other factors such as tension from hydrostatic pressure play a role in its production From his study, Lewis came to the conclusion that a susceptible state of the skin is the underlying cause of the burning pain present in different clinical conditions including erythromelalgia and suggested the term erythralgia to designate this painful redness of the skin He believed that the condition may result from almost any chronic or superficial inflammatory process He has shown that the painful redness is not due to an abnormal vasodilatation The reddened skin is the result of a relatively toneless condition of the minute cutaneous vessels and the deepening in color on dependency is due to passive congestion According to Lewis the development of erythralgia in patients with a susceptible state of the skin can be explained by pressure on the soles of the feet in walking by increased warmth resulting from accelerated blood flow associated with physical exertion by warmth from bedclothes and by tension from engorged veins in the erect posture

Diagnosis Present evidence supports the view that the condition of painful redness of the extremities described by Weir Mitchell is not a specific disease but a syndrome common to a number of distinct diseases A diagnosis of erythralgia is justified if burning pain produced by a surface temperature of 30 to 35 C by exercise warm bedclothes or dependency and relieved by rest elevation or cold is present In rare instances painful redness of an extremity may develop without any apparent cause but usually it occurs in diseases such as polycythemia vera and obliterative vascular diseases

Treatment Burning pain is relieved or greatly lessened by rest in the horizontal position and cold If the pain is severe rest in bed is indicated Bedclothes on the affected part should be light to avoid pressure and to maintain the surface temperature below the critical point for the induction of pain Acetylsalicylic acid is recommended by Allen Barker and Hines[1-3] for the relief of pain Further therapy must be directed

there was evidence of lessened oxidation, (5) the condition was not amenable to treatment

Since then others have described similar cases In 1912, Cassirer[117] gave a full review of the literature on the subject in his monograph on vasomotor and trophic neuroses In an investigation of cases of this type, Brown[1 4] determined the surface temperature of the affected part and found it raised during an attack of pain, and observed that pain occurred when the temperature reached or exceeded 33° or 34° C According to Brown attacks of local vasodilatation with increased local heat and pain constitute the basic disturbance in erythromelalgia and should not be confused with the redness and pain (painful rubor) present in thromboangiitis obliterans and arteriosclerosis He agreed with Weir Mitchell that the malady is a vasomotor disturbance of unknown etiology and a rare disease Telford and Simmons[1] believe that the condition described by Weir Mitchell may occur in a pure form, unaccompanied by any clinical signs of peripheral vascular disease, and report relief of burning pain following lumbar ganglionectomy

Burning pain produced by exercise, warm bedclothes, or standing, and relieved by cold or the horizontal position, is present in a number of different clinical conditions In an attempt to determine the mechanism of pain in patients suffering from painful conditions of the skin of the feet Lewis and Hess[1 0] reproduced burning pain and redness of the skin in normal individuals by injury to the skin from ultraviolet light burning, or freezing In areas of the skin made red and tender in this manner burning pain was produced by exposure to warmth rubbing the skin increased tension from venous engorgement or direct stretching From very carefully controlled experiments and observations they concluded that skin that is sufficiently injured in any way enters sooner or later a 'susceptible state' in which pain nerve endings are in a hypersensitive state so that the skin is hyperalgesic and its pain threshold to heat is lowered, further, that this susceptible state of the skin is not the immediate result of injury but of ensuing inflammation It is caused by the release into the skin of an unknown substance which lowers the threshold to all forms of painful stimuli[1 9]

In a study of the painful redness of the skin of the feet occurring in different diseases such as thromboangiitis obliterans, arteriosclerosis, urticaria factitia, and chronic chilblain Lewis[131] found burning pain was induced by raising the temperature of the affected part to a certain level —30° to 35° C—through vasodilatation from exercise or the application of external warmth by bedclothes and also by rubbing or stretching

tory disturbance in digital vessels which characterizes the Raynaud phenomenon

Treatment A frequent examination of the pulse should be made in all patients receiving repeated doses of ergot If pulsation is diminished or absent or if pain pallor, or cyanosis develops the drug should be stopped Cardiac and vasospastic or obliterative vascular disease should be considered contraindications to its use

As soon as systemic symptoms or local vascular manifestations of ergot poisoning are detected treatment with the drug should be discontinued and vasodilating measures instituted Injection of papaverine has been recommended but in one of our patients observed by Greenwood[180] the intravenous injection of one grain of papaverine failed to relieve the spasm Priscoline should be tried

Diseases of the Nervous System Functional vascular disturbances characterized by coldness pallor or cyanosis and later by atrophic changes in the skin and underlying tissues of the digits are not uncommon in diseases of the nervous system such as anterior poliomyelitis progressive muscular atrophy hemiplegia syringomyelia and complete section of a peripheral nerve After section and degeneration of a mixed peripheral nerve the affected part becomes pale or blue and colder than normal and is more susceptible to injury According to Lewis[8] the normal vascular response to cold or injury is altered by the section of fibers subserving a sensory axon reflex The part fails to respond to warming of the body and is persistently cold Apart from lesions causing degeneration of sensory nerves Lewis and Pickering[81] have shown that the functional vascular disturbances present in paralyzed limbs are the result of disuse and decreased blood flow and are not due to any specific disturbances in the vascular system by the lesion in the nervous system Warming the body produces a full vasodilatation in the affected part indicating a normal response of the vessels of the limb to reflex vasodilation

The first effects of disuse are a decline in local blood flow and a fall of surface temperature due to an increase in arterial tone Another factor contributing to the poor local circulation is the impairment of venous return from weakness and paralysis of muscles[181] As a result of poor local circulation the minute vessels of the skin lose tone and dilate minor injuries are slow to heal and atrophic changes develop the skin becomes smoother the pulp of the digit decreases and bones become rarefied

toward the improvement or cure of the disorder primarily responsible for the erythralgia

Ergot Poisoning A vasospastic disturbance of the extremities is an early vascular manifestation of poisoning from ergot or the alkaloid ergotamine Comfort and Erickson[18] have reviewed the literature and reported two cases of poisoning by ergotamine tartrate Vasospasm may be followed by thrombosis of vessels and gangrene of the affected part The first symptoms usually are painful muscle cramps and tingling pain in the extremities followed by sensations of coldness and numbness and by a bluish discoloration Pulsations in the dorsalis pedis or radial or both are decreased or absent Symptoms may develop in two days to two months following the daily injection of 0 5 to 1 0 minim of ergotamine tartrate If the drug is discontinued pulsations return in a couple of days in the dorsalis pedis and radial There may be a rapid and complete recovery or coldness and discoloration may persist and gangrene develop The lower limbs are more commonly affected than the upper Gangrene may be confined to the toes or fingers or may involve the foot or hand or the leg Amputation of the affected part may be necessary

In a study of the vascular responses and the histological changes in the vessels of the combs of fowl following daily injections of ergotoxine into the breast muscles Lewis[179] demonstrated that ergot produces all its effects in the comb through arterial spasm He found that the vascular spasm was unrelieved by local warming and that it was insufficient to stop the circulation through the comb and, therefore not the direct cause of gangrene He showed that the vasoconstriction caused marked slowing of the blood stream with stasis in the capillaries and nutritional changes in the proximal arteries which led to thrombosis and ultimately gangrene of the corresponding tissues

From these studies it seems clear that the early vascular manifestations of ergot poisoning are due to continued vasoconstriction of arteries in the extremities and that the persistence of coldness and discoloration after the drug is discontinued and the later development of gangrene are due to nutritional changes in arteries and capillaries resulting in thrombosis from the profound slowing of the blood stream

Diagnosis If it is recognized that ergot poisoning may be the cause of a vasospastic disturbance with absent pulsation in the dorsalis pedis and/or radial arteries which may be followed by major nutritional changes in the extremities a correct diagnosis is not difficult The condition should not be confused with the onset of the spasmodic circula

generally accepted and the condition has come to be recognized under his descriptive term

Etiology The disease occurs almost exclusively in males (99 per cent) and the onset is most common in the fourth decade of life it rarely begins before twenty or after fifty years of age It is a disease of the peripheral vascular system chiefly affecting vessels of the lower extremity It was formerly believed that the disease was confined to the Jewish race, but cases have been reported in almost all races The incidence is slightly greater among Jews and particularly those of Russian origin Brown Allen and Mahorner[187] report an incidence of over 50 per cent , The majority of our patients have been Gentiles born outside of Canada The disease is more common in temperate than in tropical climates

The cause of the disease is unknown and its rarity among women remains unexplained Erb[189] considered tobacco an important factor in the causation of intermittent claudication Silbert[169] is convinced that whatever the underlying cause smoking plays an active role in the production of the disease and that cessation of smoking is the most important therapeutic measure He observed that if patients with the disease continued to smoke they failed to improve but that prompt improvement began when they stopped smoking Barker [190] found only 1 per cent of patients with thromboangiitis obliterans non smokers Harkavy [191] Sulzberger [19] and Cooke[193] found that about 80 per cent of patients suffering from thromboangiitis obliterans gave positive skin tests to extracts of tobacco as compared with about 30 per cent in a control group of habitual smokers Sensitization tests to nicotine alone were negative Maddock Malcolm and Coller[194] found that cigarette smoking results in a decrease of skin temperature of the fingers and toes in normal men and women and in patients with thromboangiitis obliterans They showed that these changes were due to vasoconstriction and diminished blood flow caused by the nicotine in the smoke inhaled They found no consistent difference between individuals who showed skin sensitivity to tobacco extracts and those who did not Buerger who favored infection as a cause of the disease considered tobacco a predisposing but not an exciting cause of the vascular changes Oppel[195] considers hyperadrenalemia the inciting cause of spontaneous gangrene and advised left adrenalectomy in its treatment but the results of adrenalectomy have not supported the claim Telford and Stopford[87] expressed the opinion that vasospasm the result of impulses in the vasoconstrictor fibers of the sympathetic is the underlying cause of the vascular changes which

These local vascular and nutritional changes resulting from disuse are found in the paralyzed limbs of anterior poliomyelitis and the favorable effect of an increase in the local circulation on the changes present is demonstrated by sympathectomy Following sympathectomy there is a prompt, full vasodilatation of the arteries in the paralyzed limb The extremity becomes warmer discoloration lessens or disappears, ulcers heal rapidly and chilblains, if present, are relieved The immediate improvement usually is maintained, but in cases with ulceration, a recurrence may take place in cold weather [182] In a growing child, Harris[183] found an increase in the length of the paralyzed limb following sympathectomy

In diseases of the nervous system, disuse, diminished circulation, and in certain cases, sensory loss would appear to be responsible for the vascular and nutritional changes that may be present in the extremities

Treatment should be directed toward the protection of the affected part from injury and the improvement of the impaired local circulation by keeping the body warm and the application of massage and passive and active movements of the limb If these measure fail and depending upon the nature of the lesion of the nervous system, sympathectomy should be considered

Chronic Organic Vascular Disturbances

Thromboangiitis Obliterans

Introduction von Winiwarter[184] was one of the first to call attention to a circulatory disturbance of the extremities which led to gangrene but was not caused by arteriosclerosis In the case described by him in 1879 he found a chronic proliferative process in the intima of the arteries of the leg, which he believed was responsible for the obliteration of the affected vessel For this condition he proposed the name 'endarteritis obliterans' Later von Manteuffel[18] studied cases of the same type He believed that thrombosis and not intimal proliferation was the cause of the arterial occlusion Similar cases were described subsequently by others under various terms such as 'arteritis obliterans 'presenile or juvenile gangrene' 'spontan Gangran' etc In 1908 Buerger[186] published his report on the vascular lesions leading to presenile spontaneous gangrene He concluded that the primary lesion was an acute arteritis followed by thrombosis and suggested the name thromboangiitis obliterans' His clinical and pathological concept of the disease has been

disturbances of arteriosclerotic origin where the intimal lesions are more advanced and more diffuse

According to Buerger[186] the primary lesion is an acute arteritis and periarteritis the acute inflammatory process beginning in the adventitia and involving all coats of the vessel This is followed by the formation of a red thrombus which occludes the lumen of the artery Later the thrombus becomes organized into a yellowish grey firm cord often showing evidence of canalization In the chronic or healed stage of the disease the artery and adjacent veins and nerves are bound together in a fibrous cord Affected veins show a similar type of reaction

All observers are agreed as to the pathological findings in the chronic or healed lesions but opinions differ from Buerger's with regard to the early lesions Brown Allen and Mahorner[187] found a collection of lymphocytes in the adventitia and around the vasa vasorum before the development of changes in the media or thickening of the intima They believe that the disease is fundamentally a chronic inflammatory condition of the vessels but that at times an acute inflammation as evidenced by an infiltration of polymorphonuclear leucocytes is superimposed Perla[99] states that the acute lesion described by Buerger is not found in the arteries of amputated extremities In two of our amputation cases studied by Morgan[199] both acute and chronic lesions were found in different segments of the same artery In the acute stage he found an acute inflammatory reaction with cellular infiltration chiefly polymorphonuclear leucocytes involving all the coats of the artery In a third case only chronic healed lesions were present He states that all gradations between these extremes may be observed It seems likely that the earliest lesion is in the adventitia a periarteritis which ultimately affects the intima and causes thrombosis and occlusion of the affected segment of an artery The presence of acute and chronic lesions is evidence of the recurring nature of the inflammatory process

Symptoms Thromboangiitis obliterans in the great majority of cases is a disease of slow and insidious onset running a chronic course lasting from one to ten or even fifteen years Its average duration is about five years[16] Patients seek advice months or even years after the onset of symptoms In the earlier stages the vascular disturbances may become stationary or even improve More often however the disease is slowly progressive and characterized by exacerbations as new areas of arteritis and phlebitis develop If an adequate collateral circulation is not established following the involvement of each new area by occlusive thrombosis the distal circulation becomes less effective and major nutritional

induce thrombosis but later, Telford[70a] concluded that the cause is toxic rather than spastic Poisoning by ergot has been suggested as a cause but the evidence is not convincing The occupation of the individual is not a factor Exposure to cold may be an aggravating factor but is not a cause of the disease

The inflammatory character of the vascular lesions suggests infection as the causative agent but as yet no specific bacteria or virus has been found, syphilis is not responsible Buerger[18c] was able to reproduce the characteristic pathological changes in normal veins by the transplantation in man of an actively inflamed vein Horton and Dorsey[196] report the production of similar if not identical lesions by embedding segments of diseased human vessels adjacent to the femoral artery in rabbits

Klinge and Vaubel[19] regard the vascular changes as a manifestation of the allergic or hyperergic state and include thromboangiitis obliterans in the group of collagen diseases Infection and tobacco would appear to be the most likely causes of the hyperergic state but the almost exclusive occurrence of the disease in males does not support this hypothesis

Pathology Thromboangiitis obliterans is essentially a disease of the deep arteries and veins of the extremities but in about 25 per cent of cases a phlebitis of the superficial veins is present also The arteries most commonly affected are the popliteal anterior, and posterior tibial, plantar, and digital arteries in the lower extremity and, much less frequently and secondarily corresponding arteries in the upper extremity Involvement of larger arteries such as the femoral, is uncommon and occurs late in the course of the disease Lesions of the deep veins are less frequent and usually are associated with those of the adjacent artery Proof has been given both by injection[198] and by pathological examination of arteries[199] that the disease affects a short segment of a vessel The lesion may remain localized to one segment of an artery or may spread distally or proximally along the vessel, or again, more than one artery and more than one segment of the same artery may be involved at different times during the course of the disease When superficial phlebitis is present one may observe directly this manner of spread of the disease The wall of the vessel above and below the thrombotic occlusion usually shows little or no change from normal As the disease attacks adults between the ages of twenty five and fifty years, the smaller anastomotic arteries usually are free from significant arteriosclerotic changes This affords an explanation for the richer collateral circulation found in thromboangiitis obliterans as compared with that in peripheral vascular

disturbances of arteriosclerotic origin where the intimal lesions are more advanced and more diffuse

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changes in the skin of the digits make their appearance This marks the final stage of the disease

If superficial phlebitis is present, a red, tender, linear streak or a red, tender, circular area in the region of the lesion may appear In the absence of superficial phlebitis, tenderness over the deep arteries and veins probably is the only sign directly attributable to the primary arteritis or phlebitis The signs and symptoms of the disease are due essentially to impaired function and nutrition of tissues supplied by the occluded arteries

The earliest symptoms of the disease are tiredness and weakness in the calf and foot but the common early and dominant complaint is intermittent claudication a diffuse continuous aching or cramp like pain in the muscles of the calf or arch of the foot which develops with exercise disappears after a few minutes' rest, but recurs with a similar amount of exercise Gradually the distance the patient is able to walk diminishes The development of intermittent claudication indicates that the blood flow to the affected muscles is inadequate to meet their needs during exercise Pain results from stimulation of pain nerve endings in the tissue spaces of the muscles by the accumulation of metabolites normally removed by oxidation [01 b] With the development of intermittent claudication, postural color changes in the skin usually make their appearance and the foot of the affected limb feels colder than the normal limb When the leg is in the standing position or hangs down the toes and later, the whole foot become red or slightly cyanotic, if it is elevated rubor is replaced by blanching The angle of the leg at which these color changes appear can be determined, and is a measure of the efficiency of the local circulation the angle of circulatory efficiency of Buerger Rubor in the dependent position is due to engorgement of the capillaries and venules from loss of tone in these vessels and to the deficient circulation plus the effect of cold

Vasospastic disturbances may be present in thromboangiitis obliterans and may lead to a false diagnosis of Raynaud s disease [186 0] When the disease occurs in individuals who suffer from cold hands and feet, coldness of the extremities with pallor or slight cyanosis rather than rubor may be present in the early stages In a few cases attacks of discoloration with numbness upon exposure to cold, suggesting Raynaud s disease, may be present More often the patient complains of a persistent coldness of the affected foot in cold weather Allen and Brown[70] report vasospastic disturbances occurring in 30 per cent of cases of organic vascular disease It is important therefore, to examine the dorsalis pedis

and posterior tibial arteries for the presence or absence of pulsation after the patient has rested in bed in a warm room for a few hours or after immersion of the affected part in warm water The absence of pulsation is evidence of organic vascular disease

As new occlusions of the main arteries of the leg develop the distance a patient can walk without muscle pain decreases and is a guage of the rate of progress of the disease Months or years after the beginning of intermittent claudication, postural color changes in the skin of the foot appear and mark the onset of nutritional changes in the skin and subcutaneous tissue, chiefly of the digits Color changes are followed by the development of rest pain— a continuous aching or burning pain aggravated by the warmth of bedclothes, exercise or friction and partially relieved by a cool environment Rest pain increases in severity with the development of major nutritional changes such as ulcers or gangrene Buerger considered rest pain a 'tropho prodromal sign of nutritional changes resulting from relative ischemia of the affected part It is of the type already described under Erythralgia and most likely is due to low grade inflammatory changes in the digits In probably no other condition may pain be so distressing to the patient Amputation of the painful foot may be necessary to obtain relief According to Goldsmith and Brown,[05] paroxysms of severe diffuse pain which may radiate from the foot up the leg are due to an ischemic neuritis

After the development of postural color changes the nutrition of the part becomes impaired Corns and calluses are common and the toenails become opaque thickened and deformed Slight abrasions caused by ill fitting shoes or paring of corns or calluses are slow in healing and result in shallow ulcers Repeated minimal traumata which pass unnoticed by the patient probably play an important role in the development of major nutritional disturbances[204] After a mild trauma a hemorrhagic bleb may form which may heal slowly or result in gangrene Mild infections about the nails are common Too often the first appearance of an open non healing wound is after local operative treatment As pointed out by Buerger,[198] and confirmed by others the primary cause of redness and pain in the toes in obliterative vascular disease is often overlooked or misinterpreted as the result of infection Following an incision, removal of a toenail or amputation of a toe for the treatment of the supposed infection the operation wound refuses to heal leaving a fissure a shallow ulcer or a slough after amputation According to Brown Allen and Mahorner[187] major nutritional disturbances are initiated by surgical intervention in 35 per cent of the cases by other traumata in

changes in the skin of the digits make their appearance. This marks the final stage of the disease.

If superficial phlebitis is present, a red, tender, linear streak or a red, tender, circular area in the region of the lesion may appear. In the absence of superficial phlebitis, tenderness over the deep arteries and veins probably is the only sign directly attributable to the primary arteritis or phlebitis. The signs and symptoms of the disease are due essentially to impaired function and nutrition of tissues supplied by the occluded arteries.

The earliest symptoms of the disease are tiredness and weakness in the calf and foot, but the common early and dominant complaint is intermittent claudication, a diffuse continuous aching or cramp like pain in the muscles of the calf or arch of the foot which develops with exercise, disappears after a few minutes rest, but recurs with a similar amount of exercise. Gradually the distance the patient is able to walk diminishes. The development of intermittent claudication indicates that the blood flow to the affected muscles is inadequate to meet their needs during exercise. Pain results from stimulation of pain nerve endings in the tissue spaces of the muscles by the accumulation of metabolites normally removed by oxidation.[91a, b] With the development of intermittent claudication postural color changes in the skin usually make their appearance and the foot of the affected limb feels colder than the normal limb. When the leg is in the standing position or hangs down the toes and, later, the whole foot become red or slightly cyanotic; if it is elevated, rubor is replaced by blanching. The angle of the leg at which these color changes appear can be determined, and is a measure of the efficiency of the local circulation: the angle of circulatory efficiency of Buerger. Rubor in the dependent position is due to engorgement of the capillaries and venules from loss of tone in these vessels and to the deficient circulation plus the effect of cold.

Vasospastic disturbances may be present in thromboangiitis obliterans and may lead to a false diagnosis of Raynaud's disease.[186, 209] When the disease occurs in individuals who suffer from cold hands and feet, coldness of the extremities with pallor or slight cyanosis rather than rubor may be present in the early stages. In a few cases attacks of discoloration with numbness upon exposure to cold, suggesting Raynaud's disease, may be present. More often the patient complains of a persistent coldness of the affected foot in cold weather. Allen and Brown[210] report vasospastic disturbances occurring in 30 per cent of cases of organic vascular disease. It is important, therefore, to examine the dorsalis pedis

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descending coronary artery was completely occluded by an old thrombus which had become organized and canalized Allen and Willius [08] found no definite relationship between thromboangiitis obliterans of the extremities and disease of the coronary arteries The reported cases of thrombosis of the aorta have shown arteriosclerosis and thrombosis From observations based on clinical symptoms of vascular disturbances affecting the cerebral, coronary, and abdominal arteries in patients with thromboangiitis obliterans of the extremities and a review of the literature, Barron and Linenthal [09] considered that thromboangiitis obliterans is a generalized disease that may affect any part of the arterial tree In a report of eleven cases of thromboangiitis obliterans with cerebrovascular complications but without any histological examination of the cerebral vessels Hausner and Allen[410] state It is now known that thromboangiitis is a disease which is not limited to the extremities' The evidence from the histological examination of vascular lesions of the brain heart and abdomen does not warrant the conclusion that thromboangiitis obliterans is a generalized vascular disease

Diagnosis Thromboangiitis obliterans should present little or no difficulty in diagnosis if one but bears the disease in mind as a likely cause (1) of muscle pain in calf or foot developing with exercise and relieved by rest in a male under fifty years of age coupled with absent pulsation of the posterior tibial and dorsalis pedis arteries, (2) of postural color changes rubor on dependency and blanching on elevation of the limb (3) of sense of coldness of a foot (4) of rest pain with redness confined to one or more digits (5) of slow healing of minor abrasions of foot or gangrene of a digit A history of intermittent claudication in association with superficial phlebitis in a male under fifty years of age may be considered diagnostic of thromboangiitis obliterans

Aching pain in the foot with exercise often is diagnosed wrongly as fallen arch flat foot rheumatism or arthritis As already mentioned pain and redness of one or more toes often are attributed to infection and treated by operation before obliterative vascular disease has been excluded as a cause of the symptoms If the palpable arteries in the extremities were examined carefully for the presence or absence of pulsation in all patients fewer mistakes in diagnosis and treatment would be made Pulsations are present in functional but absent or diminished in obliterative vascular disturbances The Pachon oscillometer or a Tycos recording sphygmomanometer may be used for the detection of pulsations in the deep arteries of the extremities but are of limited value in the diagnosis of obliterative arterial disease The injection of radio opaque sub-

30 per cent, and occur without known cause in 35 per cent

The superficial as well as the deep veins may be affected and superficial phlebitis often is present, in fact, superficial phlebitis may be the first manifestation of the disease The long saphenous vein and its tributaries are most commonly affected The phlebitis, involving a short segment of vein may manifest itself as a red, tender streak along the vein or as a red tender nodular area at one of the valves After one to three weeks the acute manifestations subside, leaving a firm cord or nodule From time to time other segments of the vein are affected

Absent or diminished pulsation in the dorsalis pedis or posterior tibial artery, or in both is almost a constant finding in thromboangiitis obliterans of the lower limb and is found in the early stages of the disease In rare instances occlusive thrombosis may be confined to more distal arteries in the foot and pulsation may be present in the dorsalis pedis and posterior tibial [0]

At the onset, symptoms of the disease usually are confined to one leg but sooner or later the other leg and less often, the upper extremities are affected Thromboangiitis obliterans rarely begins in the upper extremities and the clinical manifestations are less marked and the disease tends to progress more slowly Absence of pulsation in the ulnar or radial arteries may be found without symptoms

Rarely thromboangiitis obliterans may attack the spermatic vessels producing symptoms suggestive of tuberculous epididymitis Buerger and McGregor and Simson [0] each report a case in which acute lesions characteristic of thromboangiitis obliterans were found but there were no signs or symptoms of the disease in the extremities These two cases are the only ones known to the writer in which acute and chronic lesions of thromboangiitis obliterans have been found in vessels other than in the extremities Telford [98] refers to one case with lesions characteristic of thromboangiitis obliterans in the coronary, and Perla [90] to one case with lesions in the coronary resembling thromboangiitis Buerger[186] examined the vessels from four fatal cases of thromboangiitis obliterans of the extremities two dying of coronary disease and two with thrombosis of the aorta Lesions typical of thromboangiitis were found only in the vessels of the extremities In a similar case Klotz [97] found three types of lesions in the arteries of the body typical lesions of thromboangiitis in the distal arteries of the upper and lower extremity a progressive mesarteritis and endarteritis of the aorta with thrombosis, and an endarteritis of the coronary renal cerebral and iliac arteries with no inflammatory reaction in the media or adventitia A branch of the left

occluded artery or arteries is adequate to meet their metabolic needs under varying conditions, no signs or symptoms develop Usually, however, *the collateral circulation becomes inadequate in the affected muscles* with exercise and in the skin of the digits on exposure to cold and signs and symptoms of an insufficient local circulation develop muscle pain on exercise and coldness of one or more digits As new areas of occlusion occur there is a further impairment of the collateral circulation with exacerbation of symptoms the walking distance without muscle pain decreases, the skin and subcutaneous tissue of the digits become more ischemic and more sensitive to trauma and major nutritional disturbances rest pain ulceration and gangrene develop

As no known method of treatment can alter the natural course of the occlusive process in the main arteries of the leg the ultimate results of treatment must depend chiefly on the effectiveness of the collateral circulation It would seem desirable therefore to consider factors affecting the natural development of the anastomotic circulation and its effectiveness in occlusive arterial diseases before discussing methods of treatment to maintain or augment blood flow through these channels

It has long been known that the femoral artery of a young individual could be ligated and the nutrition of the extremities be maintained through the collateral circulation In wounded soldiers, Makins[11] observed that a weak radial pulse returned in three to four days after ligation of the brachial artery but that the posterior tibial artery remained impalpable for weeks after ligation of the femoral artery Richards[83] has stated that the radial pulse is often palpable in twenty four hours after ligation of the brachial or axillary arteries and the posterior tibial pulse in seven to ten days after ligation of the femoral The earlier return of the pulse in the arm than in the leg was an indication of the richer collateral circulation now known to exist in the upper extremity and accounts for the rare occurrence of serious nutritional changes in the upper extremity after an acute embolic occlusion of a large artery Recently Shepherd[2] has recorded the calf blood flow by a plethysmograph before during and after the occlusion of the femoral artery in young healthy adults by a mechanical compressor He found that the resting calf blood flow after an initial drop to zero returned to the normal resting level in about two minutes from the onset of the compression which was maintained for eight to ten minutes This shows that the vasodilation of anastomotic channels supplied a blood flow to tissues affected by the occlusion which was adequate for their metabolic needs under resting conditions He also studied the effect of release of vas

stances for the demonstration of arterial occlusions is not indicated in thromboangiitis obliterans

Ninety-five per cent of the cases of chronic obliterative vascular disease are due to thromboangiitis obliterans and to arteriosclerosis [0] The former usually occurs before forty years of age and peripheral vascular disturbances of arteriosclerotic origin rarely develop before forty Superficial phlebitis is absent in disturbances due to arteriosclerosis and often present in thromboangiitis obliterans Difficulty in differential diagnosis is confined to a small group of cases

Prognosis Prognosis must be based on the rate of progress and the severity of the signs and symptoms of the disease and the condition of the digits The distance a patient can walk without being stopped by muscle pain is an index of the degree of impairment of the blood supply to the muscles of the leg and foot from occlusion of their main arteries It is also an index of the blood supply to the limb as a whole Intermittent claudication may incapacitate a patient from work demanding walking distances which cause muscle pain but it does not endanger life The really distressing and crippling disabilities in the disease result from impairment of the cutaneous circulation to the foot which may develop months or years after the onset of intermittent claudication, depending on the rate of progress of the occlusive process The disease is usually slowly progressive and characterized by exacerbations of symptoms as new occlusions of main arteries occur It is rarely severe and progressive from the onset of intermittent claudication The early nutritional changes in the skin and subcutaneous tissue of the toes are due to the deficient collateral circulation resulting from multiple occlusion of the main arteries but the major nutritional disturbances ulceration and gangrene result from damage to the relatively ischemic tissue from minor and major traumas Loss of a toe or a leg, or even life may result from gangrene When the disease affects the main arteries of the upper extremity, major nutritional disturbances of the fingers are rare

Treatment The primary arterial lesions which terminate in segmental occlusions of the main arteries of the leg and foot cause no distress to the patient and heal spontaneously No method of treatment for the prevention of these lesions is known The disturbances causing distress and requiring treatment result from ischemia of tissues—muscle skin, and subcutaneous tissue supplied by the occluded main arteries These tissues become dependent on the collateral circulation for their blood supply If the collateral circulation in tissues supplied by the

cating a partial or complete occlusion of these vessels—from arterio sclerosis and thrombosis After a similar segmental occlusion of the popliteal artery the collateral circulation is less effective claudication is more severe and nutritional changes in the skin are more common

In occlusive arterial disease of arteriosclerotic origin sclerotic changes are present in both the main and the small arteries of the leg and foot and a thrombus of varying length is present in one or more of the main arteries when signs and symptoms of occlusive arterial disease develop Owing to structural changes the collateral arteries no longer respond to maximal dilatation on warming the body or spinal anesthesia Nutritional changes in the skin and subcutaneous tissue of the digits are common and, unlike the course of thromboangiitis obliterans often develop be fore the onset of intermittent claudication

In thromboangiitis obliterans the primary occlusive process in the main arteries usually develops in males under forty years of age and both the main arteries and the smaller arteries of the collateral circulation are relatively free of sclerotic changes maximal dilatation occurs on indirect heating or spinal anesthesia The occlusive process does not affect directly the collateral arteries but the occlusions may block the mouths of these vessels at their origin and thereby limit the number of proximal arteries available for the formation of an anastomotic circula tion distal to the occlusion

From these observations it is evident that the presence or absence of sclerotic changes in main arteries and in those forming the collateral circulation the presence of single or multiple occlusions in the main arteries, and the site of the occlusion are important factors affecting the natural development of the collateral circulation and in determining its effectiveness in meeting the metabolic needs of tissues supplied by the occluded main artery or arteries The efficiency of the collateral circu lation will also depend on the metabolic requirements of muscle skin and subcutaneous tissue and on the normal control of their blood supply It is well known that the normal blood flow to the skin and subcutaneous tissue is regulated chiefly by sympathetic vasoconstrictor fibers and that the release of vasomotor tone in a limb by reflex vasodilation or spinal anesthesia produces an increase in blood flow much greater than the nutritional requirement of the skin and subcutaneous tissues of the foot during rest and activity In patients with occlusive arterial disease due to thromboangiitis obliterans or arteriosclerosis Kunkel and Stead [15] found that the maximum blood flow to the foot after release of vaso motor tone had to be reduced to one third the normal level before signs

omotor tone in collateral arteries and found that the calf blood flow was increased two to four times by indirect heating and one and a half to two times by the intravenous injection of 500 milligrams of the ganglion blocking agent tetraethylammonium bromide These findings afforded proof that the tone of arteries forming the collateral circulation in occlusive arterial disease is under the control of the sympathetic nervous system, and they are in accord with the experimental and clinical observations of others Mulvihill and Harvey [1] showed that the cooling of an extremity of a dog, which had persisted for several hours after ligation of the external iliac, could be relieved promptly by sympathectomy After an embolic occlusion of the femoral artery in man Gage and Ochsner[13] observed the disappearance of numbness and the return of normal color and surface temperature of the extremity following novocain block of the lumbar sympathetic ganglia

The initial dilation of anastomotic channels between arteries proximal to a chronic arterial occlusion of a main artery is followed by an increase in their length and caliber Lewis [6] quotes Nothnagel as stating that actual growth has been detected as early as the sixth day and may be conspicuous in six to eight weeks Arteriographic studies have demonstrated the marked enlargement of these vessels that may develop following a complete thrombotic segmental occlusion of the aorta common iliac, or external iliac arteries The maximal development takes at least six months and probably a year or longer

In chronic occlusive arterial disease probably the most effective collateral circulation in the lower extremity develops following a chronic segmental thrombotic occlusion of the common or external iliac arteries in a young individual the main arteries distal to the occlusion remaining patent and free of occlusions In a case of a chronic complete occlusion of the external iliac artery reported by Boyd and Jepson, [14] intermittent claudication was the presenting symptom but the foot remained warm and nutritional changes in the skin were absent Arterial pulsations in the leg were present, indicating the spontaneous development of a rich collateral circulation and blood flow in the main arteries distal to the occlusion This was confirmed by an arteriogram In occlusions of this type intermittent claudication of the thigh hip or calf is always present but significant nutritional changes in the skin and subcutaneous tissue of the digits are usually absent When present they appear months or years after the onset of intermittent claudication and usually occur in older individuals with peripheral arteriosclerosis Pulsations in the posterior tibial and dorsalis pedis arteries are diminished or absent, indi-

should rest with the superficial veins not collapsed or distended at an angle slightly below heart level Keeping the leg in a dependent position favors the development of edema The heel should be protected from pressure on a mattress and the toes by bedclothes Hot water bottles or electric pads should never be applied to an ischemic extremity Heat applied in this manner not only increases the local metabolism and blood flow requirement of the ischemic tissue but may produce a burn which will be slow to heal The patient should receive plenty of fluids and a balanced diet A good sleep at night particularly at the beginning of treatment is important A combination of acetylsalicylic acid phenacetin and codeine may be given to lessen rest pain and a barbiturate at bed time to induce sleep The use of anticoagulants is not indicated in the treatment of thromboangiitis obliterans On account of the increased vasoconstriction resulting from smoking and the possible deleterious effect of tobacco on the course of the disease one should insist on the cessation of the use of tobacco by the patient

If abrasions ulcers, or gangrene of the digits are present, the foot should be protected by a cradle and the affected part treated with a warm but not hot solution of boracic acid in the form of a wet compress or a foot bath two or three times a day This also serves to control any coexisting fungous infection of the toes until it subsides and a non irritating dusting powder can be applied If a local cellulitis in the region of ulcerative or gangrenous tissues or paronychia is present local treatment should be combined with intramuscular injections of penicillin which is safer and more effective than sulphonamides Topical applications of antibiotics and chemotherapeutic agents are of little value in the treatment of infections in ischemic digits Apart from massive gangrene which may require early amputation, other open lesions should be given a prolonged trial of conservative treatment before operation is advised

Increased vasoconstrictor tone of the smaller arteries and strong arterioles as well as the occlusive thrombosis of the main artery contribute to the deficient cutaneous circulation of the foot At the beginning of treatment it is advisable therefore to measure the rise in the surface temperature of the digits after maximal vasodilation from immersion of an unaffected arm at 43 C for thirty minutes This gives one an indication of the part played by vasoconstriction and by structural vascular changes in causing the deficient local circulation of the digits

Care of the feet is important Chronic impairment of the cutaneous

or symptoms of major nutritional changes occurred, but that incapacitating intermittent claudication might be present although the blood flow in the foot was as great as in many normal individuals It is now generally accepted that the increased blood flow in the capillary bed of skeletal muscles during exercise is due to the release of metabolites from active muscle fibers and is independent of the sympathetic nerves As further evidence of the difference in the control of blood flow in muscle and in skin exercise raises the temperature of active muscles with little change in the surface temperature of the digits, but the reverse occurs after reflex vasodilation Grant[17] found, and others have confirmed, that active skeletal muscles require a blood flow twenty to thirty times the resting muscle blood flow and Shepherd[27] has shown that the maximal increase in blood flow to muscle through the collateral circulation after the release of vasomotor tone was only four times the resting flow, a level much below the normal muscle blood flow during moderate exercise These studies demonstrate that the collateral circulation in occlusive arterial diseases cannot be equally efficient in meeting the normal nutritional requirements of active skeletal muscles and of skin and subcutaneous tissues of the foot It seems obvious then that methods of treatment proposed for the improvement of the collateral circulation cannot be equally effective in relieving the effects of ischemia of active skeletal muscle and of skin and subcutaneous tissue of the digits

Treatment presents three main problems (1) the relief of rest pain and the healing of ulceration and gangrenous tissue in the foot, chiefly the digits, (2) the prevention of trauma—mechanical, thermal, or chemical—to the relatively ischemic digits, and (3) the improvement of the collateral circulation

Medical Treatment Treatment should begin with rest in bed, preferably in hospital This is essential in advanced cases with rest pain, ulceration, or gangrene and is advisable in all cases for more accurate diagnosis and assessment of the disability and for the education of the patient regarding the nature of his disease and details of treatment which he must carry out Rest lessens the metabolic needs of ischemic tissues and a warm room and adequate bedclothes keep the body and extremities warm, thereby preventing any central or local vasoconstriction from exposure to cold In addition to adequate coverings to keep the body and extremities warm the cutaneous circulation of the foot may be kept near the normal vasodilation level by the use of a cradle under thermostatic control heated by electric light bulbs The environmental temperature of the leg should not be higher than 33 3° C (92° F) [716] The leg

12 Never use any antiseptic drugs on your feet except boracic acid (one teaspoonful diluted in a pint of water) without the advice of your physician
13 Go to bed and call your doctor upon noticing any abrasions pain, or redness in the foot
14 If your eyesight is poor have a member of your family examine your feet once a week
15 If you are a diabetic adhere strictly to the treatment advised for that

After a week s observation for accurate diagnosis and assessment of the disease and education of the patient regarding prevention of trauma patients with intermittent claudication but no unhealed lesions of the digits or rest pain should be allowed to return home and resume work if the affected part can be protected from cold and trauma and walking kept within the distance causing muscle pain A change of occupation may be necessary but change of residence to a warmer climate can be of little advantage to a patient with thromboangiitis obliterans

Almost all patients with rest pain ulcers or gangrene slowly improve under the treatment outlined As major nutritional changes in the digits result in most instances from trauma on the relatively ischemic tissues the relief of rest pain and the treatment of open lesions should be accelerated by an increase in blood flow through the collateral circulation The simplest medical measure for producing a maximal blood flow in the cutaneous circulation of the feet for several hours each day without increasing the metabolism of the ischemic tissue is reflex vasodilatation by warming one or more extremities at 43 C Learmonth [174] recommends placing the hand and forearm in a box heated by electric light bulbs or an electrically heated glove [176] and reports acceleration of healing of open lesions Brown and Allen [18] suggested the use of an electrically heated sleeve The heating unit consists of a fine copper wire woven into fireproof cloth with thermostatic control of the temperature Owing to difficulty in the manufacture of this unit it has not been given an adequate trial Another method of treatment which has been shown to be effective in the relief of rest pain and the healing of ulcers is foreign protein therapy In 1923 Goodman and Gottesman[219] reported that the intravenous injection of foreign protein relieved rest pain and improved the appearance of the extremities in thromboangiitis obliterans Brown[74] gave this method of treatment an extensive trial using typhoid vaccine as the foreign protein and showed that the fever reaction induced by the foreign protein resulted in an increased blood

circulation from the occlusive thrombosis of main arteries results in minor nutritional changes in the skin and subcutaneous tissues of the foot and lowers the resistance of these tissues to trauma Proper hygiene of the feet and protection from trauma will prevent, in most instances, the development of major nutritional changes such as ulceration and gangrene of the toes If they do develop, recognition of their primary vascular origin and application of appropriate treatment will save many limbs from amputation Patients should, therefore, be instructed as to the nature of the disease and the importance of proper care of the feet and be given a list of instructions such as the following

1 Wash your feet every night with castile (face) soap and warm water, dry completely with a soft towel without rubbing the skin
2 Apply rubbing alcohol (70 per cent) and allow the feet to dry then apply a liberal amount of vaseline or purified lanolin including the toenails and gently massage the feet
3 Cut your toenails only in a very good light and only after washing the feet cut the nails straight across
4 Do not pare corns or calluses or apply corn plasters To remove a corn or callus soak the foot for half an hour in warm water to which baking soda (one tablespoonful to a quart of water) has been added Upon drying the feet the loose dry skin may be removed by light friction with a clean pumice stone
5 Wear loose fitting bed socks at night Do not use hot water bottles electric heating pads etc
6 *Always keep your feet and extremities warm,* wear soft woolen socks and change them daily
7 *Wear properly fitted shoes* that are long enough not too tight and fit at the ball and heel of the foot Shoes made from soft stout leather with a moderately thick extension sole and a high box cap to protect the sole of the foot and the toes are the most satisfactory New shoes should be worn only half an hour daily until broken in
8 Avoid exposure to extreme cold
9 Do not wear circular garters or sit with your legs crossed both tend to obstruct the circulation of blood in the legs
10 Avoid walking the distance which brings on a sensation of fatigue or pain in the muscles of the leg or foot Avoid standing for long periods
11 Do not use tobacco

1 Never use any antiseptic drugs on your feet except boracic acid (one teaspoonful diluted in a pint of water) without the advice of your physician
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flow of the digits with relief of rest pain in variable degrees for one to ten days and more rapid healing of ulcers, but had little or no effect on intermittent claudication Experience has shown that foreign protein therapy is of definite value in the treatment of patients with rest pain and open lesions of the digits The usual course of treatment is six to twelve intravenous injections of T A B vaccine at intervals of four to seven days The usual dose of the vaccine is 15 to 30 million with an increase of 25 million for each dose until a maximum of 300 million is reached A febrile reaction producing an oral temperature of 101° to 102° F (38 3° to 38 9° C) is desirable, and the dose should be regulated accordingly Heavy chills should be avoided The adrenolytic and sympatholytic drug Priscoline produces a vasodilation in the digits, usually equal to that from reflex heating and with little change in blood pressure One may expect to maintain a maximal vasodilation of the collateral circulation from the oral administration of 25 to 50 milligrams of Priscoline every four hours if the patient tolerates the drug in effective dosage After a few weeks' treatment, partial or complete relief of rest pain and the healing of ulcers but no significant improvement in walking distance has been reported The drug is worthy of trial as a temporary adjunct to general medical treatment of rest pain and open lesions Continued treatment with Priscoline cannot be recommended as a practical measure for inducing persistent vasodilation of the cutaneous circulation

Medical treatment, except in cases of extensive gangrene, should be continued until superficial ulcers heal and a line of demarcation of gangrenous digits is established or open lesions fail to improve if one is to reduce the incidence of major amputation When extensive gangrene is present immediate amputation may be necesary

Many other methods of medical treatment have been suggested for the treatment of occlusive arterial disease from thromboangiitis obliterans and arteriosclerosis Among these mention may be made of Buerger's exercises, injections of Ringer's sodium citrate or hypertonic salt solution diathermy, vitamin E alternate suction and pressure therapy (pavex—passive vascular exercises) intermittent reactive hyperemia (intermittent venous occlusion) and Sanders' oscillating bed Buerger[186] recommended that the leg be elevated and lowered for short intervals several times a day over a long period of time as an exercise for the improvement of the collateral circulation Buerger's method of postural treatment, as modified by Allen,[170] is briefly as follows With the patient

horizontal in bed, the leg is elevated to 45° above the horizontal and allowed to rest on a support until a complete blanching occurs the period of time being one to three minutes As soon as blanching is established (average time two minutes) the patient allows the foot to hang down over the edge of the bed for two or three minutes or one minute after a good red color is established in the foot While in this position both feet are turned inward and outward, ankles flexed downward and upward, and the toes moved The patient then returns to the horizontal position in bed with the extremities in a heated cradle for a period of five minutes The three positions complete a cycle which should be repeated immediately for six cycles After an hour's rest in bed the exercises should be repeated two to six times a day depending on the condition of the patient They should be continued during the patient's stay in hospital, and after his return home if the condition of his feet does not warrant his walking This method of treatment is unsuited for patients with severe rest pain, ulceration, or gangrene It is doubtful if this treatment significantly augments the spontaneous development of the collateral circulation in thromboangiitis obliterans

Sanders'[1] oscillating bed is another method of postural exercise treatment It has the advantage that passive filling and emptying of the cutaneous vessels of the extremity takes place without effort on the part of the patient and the only contraindication to the treatment is massive gangrene and severe infection Unfortunately the bed is not simple to operate and it is expensive Barker and Roth[2] report that the most striking therapeutic effect is the relief of rest pain during the treatment With prolonged treatment for several days or weeks the relief of rest pain persisted for at least six months in one third of the cases treated No effect on intermittent claudication was observed Horton[3] states that the patient must be kept in an environmental temperature of 82° F or above during treatment to get rid of vasospasm in the feet It would appear that the favorable effects of the treatment may be due more to a warm environment than to the postural exercise

Two other mechanical measures—alternate suction and pressure and intermittent venous occlusion—have been proposed for the improvement of the collateral circulation in occlusive arterial diseases Landis and Gibbon[4] and Herrmann and Reid[5] working independently, devised apparatus for studying the effects of alternate negative and positive pressure on the circulation of the extremity They showed that alternate suction and pressure produces a rise in surface temperature of the foot

and abolishes rest pain during the treatment and accelerates the healing of open lesions if the treatment is continued Landis and Hitzrot [6] recommended treatment for one to two hours once or twice a day, then three times a week and finally once a week, the period of treatment depending on the improvement and symptoms Herrmann, who designed the apparatus (Pavex—passive vascular exercise), recommended a course of treatment of four to six hours daily with a total period of 100 hours Their results in the treatment of thromboangiitis obliterans were disappointing Contraindications to the use of this treatment are superficial phlebitis, extensive gangrene and local infection Experience has shown that the best results from this treatment have been obtained in acute arterial occlusions As stated by Landis and Hitzrot alternate suction and pressure therapy may be of service by increasing blood flow temporarily during episodes of rest pain or ulceration so that time is gained for the development of adequate collateral blood flow, but they should not displace other conservative methods of treatment

It has long been known that the removal of a tourniquet used to control hemorrhage while operating on a limb, is followed by reactive hyperemia Lewis and Grant demonstrated that a temporary occlusion of the arterial or venous supply of a limb is followed by a state of vasodilation which lasts one half to three-quarters as long as the pressure period of occlusion They also noted that the reaction was greater at higher environmental temperatures Based on these observations Collens and Wilensky [8] devised an apparatus for the application of intermittent venous occlusion in the treatment of peripheral vascular disease After a course of treatment consisting of venous occlusion for alternating periods of two minutes for twelve hours per day for one to two weeks and then two hours three or four times a week, they report relief of rest pain healing of ulcers and increase in walking distance in the majority of patients with chronic occlusive arterial disease but the treatment was combined with rest in bed in an environmental temperature of 95° F and cessation of smoking Brown and Arnott [29] observed that any favorable effects of the treatment in thromboangiitis obliterans were nullified by the continuation of smoking by the patient Hamilton and Wilson [30] found no significant difference in the improvement in exercise tolerance of patients with intermittent claudication treated by rest in bed alone as compared with those by intermittent venous occlusion with rest in bed necessitated by the treatment They concluded that intermittent venous occlusion was valueless for the treatment of intermittent claudication

Mayesima[31] observed an increased viscosity of the blood in thromboangiitis obliterans and Koga[23] advocated the injection of Ringer's solution and Ginsberg[33] sodium citrate to reduce the viscosity Any deleterious effect of increased viscosity is of minor importance in the disease and it can be controlled by an adequate intake of fluids Silbert[34] has recommended the intravenous injection of hypertonic sodium chloride solution as a routine treatment 150 cubic centimeters for the first injection and 300 cubic centimeters for each subsequent injection At first the injections are given three times a week and later twice a week A course of treatment varies from six weeks to two years He reported improvement in 83 per cent of cases as evidenced by cessation of rest pain healing of ulceration and increase in walking distance without muscle pain Amputation was required in only 7 6 per cent of 434 patients treated However the injection treatment in patients with open lesions was combined with rest, bland treatment of ulceration the section of peripheral nerves for the relief of severe rest pain (25 per cent of cases) and cessation of smoking Samuels[7] a strong supporter of hypertonic saline therapy recommends the intravenous injection of 300 cubic centimeters of to 3 per cent sodium chloride solution every other day until ulceration or gangrene has healed and then at longer intervals depending on the severity of the condition The saline treatment was combined with rest in bed bland treatment of areas of ulceration and gangrene anesthetic ointment for the relief of rest pain and cessation of smoking He reports healing without amputation in twelve cases of ulceration and gangrene and that less than 1 per cent of 300 patients receiving the treatment required amputation As satisfactory results in treatment were obtained only in patients who stopped smoking and the injection treatment was prolonged and combined with other methods known to influence favorably the relief of rest pain and the healing of open lesions these favorable results would appear to be due more to the associated measures than to the hypertonic saline

Tissue extracts and vitamin E have been recommended for the treatment of intermittent claudication in obliterative vascular disease In 1930 Frey[36] reported that a new internal secretion of the pancreas discovered by Frey and Kraut and manufactured under the trade name Kallikrein, later Padutin relieved the pain of angina pectoris and intermittent claudication Abramson *et al*[23] found no increase in blood flow of forearm hand leg or foot after an intramuscular injection of 4 biological units of Padutin Barker *et al*[38] studied the effect of Padutin and of a muscle extract, Myosoton in peripheral vascular disease After

one intramuscular injection of 3 cubic centimeters of Padutin or 2 cubic centimeters of Myosoton the claudication time was doubled for two to seven days and then gradually returned to the original claudication time They found no evidence of vasodilation of the cutaneous circulation Allen *et al* [1 3] obtained the best results from Padutin in moderately severe intermittent claudication and attributed its therapeutic effect to its influence on the metabolism of the ischemic muscle They recommend a daily intramuscular injection of 5 cubic centimeters for one to two weeks, then once a week for the next four weeks, and once a week for the next month Shepherd [39] measured the exercise tolerance by an ergograph and the blood flow of the calf, using a plethysmograph, in eight patients with intermittent claudication before, during, and after twelve to twenty-one weeks' treatment with Padutin He found no evidence that the drug relieved the claudication or increased the calf blood flow after exercise Two patients said their walking distance was increased from two hundred yards to a mile during treatment but the ergograph measurement showed no increase in claudication time and there was no change in the post-exercise blood flow

Shute *et al*, in 1947 suggested the administration of vitamin E (alpha tocopherol) in the treatment of angina pectoris, and of peripheral vascular disease in 1948 [10] Controlled studies by several observers have not confirmed the favorable claims in angina pectoris In 1949 Boyd *et al* [241] reported that fifty-seven of seventy-two patients (8. 2 per cent) with moderately severe intermittent claudication (Type II, Boyd) had freedom from pain or minor discomfort after walking half a mile at the patient's normal pace following the daily administration of 400 milligrams of synthetic alpha tocopherol (Ephynal, Roche) for three months They also reported that similar results were obtained in forty seven of fifty-two (90 per cent) of Type II claudicants after lumbar sympathectomy Hamilton *et al* [30] determined the exercise tolerance by the method of Wayne and Laplace [4] of forty-one patients with intermittent claudication (Types II and III, Boyd) at fortnightly intervals before during, and after three months' treatment with vitamin E The patients were divided into two similar groups one group received 450 international units daily of natural vitamin E in gelatin-coated capsules, and the other group gelatin coated capsules of arachis oil They found that the beneficial effect of vitamin E was not appreciably greater than that of arachis oil, and concluded that vitamin E is of no value in the treatment of intermittent claudication

Edwards *et al* [13] treated two patients having thromboangiitis oblit

erans accompanied by small ulcerations, rest pain, and intermittent claudication with testosterone propionate, and reported healing of ulcers relief of rest pain and marked improvement in walking ability Hamilton and Wilson [30] treated nine patients with occlusive arterial disease for periods of three to six weeks with 5 milligrams of methyl testosterone twice daily by mouth, tested their exercise tolerance before, during, and after the treatment, and found no increase in their exercise tolerance

It seems clear that none of the methods proposed for the treatment of intermittent claudication augments to any significant degree the blood flow resulting from the natural development of the collateral circulation

Surgical Treatment Treatment by surgical procedures is indicated for gangrenous lesions severe infections, the relief of intractable rest pain, and for inducing a persistent vasodilation of the primary and collateral circulation of the affected extremity by sympathectomy

Clinical experience in the treatment of thromboangiitis obliterans in the past three decades has indicated that cessation of smoking proper hygiene and protection of the feet from cold and minor and major trauma, with rest in bed in a warm environment for patients with open lesions and a bland local treatment of these lesions have decreased the incidence of major nutritional changes in the digits and of amputations especially major amputations In 1932 Adson and Brown [44] reported definite improvement in 56 per cent of patients following active medical treatment and a decrease from 25 to 14 per cent in the incidence of amputation In a series of cases treated by conservative methods, Silbert [31b] reports the incidence of amputation as 7 6 per cent In 20 per cent of patients treated at the Mayo Clinic, gangrene was present on admission, it was found that gangrene had followed therapeutic procedures for painful toes or feet in 35 per cent and of this group 50 per cent required amputation for gangrene induced by ill advised treatment If this cause of gangrene is eliminated by the early recognition of obliterative vascular disease as a cause of painful toes or feet and appropriate medical treatment instituted a further reduction in the incidence of amputation should result

Control of infection in thromboangiitis obliterans is rarely a serious problem Minor open lesions usually respond to treatment by rest and the application of moist compresses of a saturated boracic solution or Dakin s solution in a dilution of 1 12 or 1 6 If extensive gangrene or a local cellulitis in the region of ulceration and gangrene are present

local treatment should be combined with the intramuscular injection of penicillin

Rest pain is a dominant symptom in cases of ulceration and gangrene of the digits In most instances the pain can be partially relieved and the healing of open lesions made possible by rest and medical treatment In certain cases a severe rest pain persists It may be relieved by morphine but the prolonged use of habit-forming drugs is contraindicated Surgical procedures other than amputation advocated for the relief of uncontrollable rest pain in occlusive arterial disease are alcohol injections crushing and section and resuture of one or more of the peripheral nerves in the leg depending on the location of the pain in the foot especially the toes Laskey and Silbert [4] recommended section and immediate resuture of the nerves Smithwick and White [46a] first proposed alcohol injection of one or more of the peripheral nerves at the junction of the middle and lower third of the leg but later found that crushing[46b] in a hemostat was an easier operation and avoided the danger of alcohol spilling into tissues with a deficient blood supply They recommend the crushing operation in preference to section and resuture for the relief of severe rest pain as a preliminary to sympathectomy in patients with ulceration and gangrene but state that the operation requires careful technique and asepsis and that nobody should attempt it until he is thoroughly familiar with the course of the nerves to be crushed For details of the operation, the reader is referred to the original articles

According to Smithwick and White, the beneficial effects of the crushing operation are the relief of the severe pain and the consequent improvement in the general condition of the patient, the painless dressing of necrotic lesions and an increase in the blood flow with acceleration of healing in these lesions It is their impression that this procedure has halved the number of necessary major amputations and more than doubled the number of successful amputations The experience of others with this method of treatment has been less satisfactory and it has not come into general use in the treatment of occlusive arterial disease De Takats *et al* [4] reported that he abandoned the treatment because of the difficulty of complete desensitization, the painful paresthesia occurring during the period of return of sensation and the dangers of unnoticed trauma in the insensitive area Allen *et al* [1 3] found amputation inevitable in most cases of ulceration and gangrene with uncontrollable rest pain after a thorough trial of medical treatment Even granted that rest pain is relieved in this type of case, there are certain

unfavorable effects known to result from a complete denervation of peripheral cutaneous nerves even in a normal extremity that may outweigh the immediate good effects of treatment apart from the relief of rest pain The site of rest pain usually one or more toes is in relatively ischemic tissue already susceptible to the effects of trauma After interruption of the afferent sensory fibers rest pain may be relieved and the dressing of necrotic lesions facilitated but the denervated area is insensitive to painful stimuli and more prone to injury The interruption of efferent sympathetic vasoconstrictor fibers which are distributed with sensory fibers releases vasomotor tone in the vessels of the denervated area and the surface temperature rises to a maximal vasodilation level if the vessels are free of structural changes The increase in blood flow accelerates healing of open lesions but the increase in surface skin temperature is not maintained as after a lumbar sympathectomy As has been shown by Lewis and Pickering[84] and confirmed by Richards[83] a completely denervated area after section of a peripheral cutaneous nerve becomes colder than before the interruption in about three weeks According to Lewis and Pickering this change in surface temperature corresponds in time to degeneration of the sensory fibers and disappearance of the sensory axon reflex responsible for the spreading flare in the triple response of Lewis At this stage the histamine flare is absent in the skin of a completely denervated digit and it no longer responds in a normal manner to reflex heating Its temperature becomes dependent on the environmental temperature and unless the foot is kept in a warm environment the denervated part is persistently cold It has been shown that this condition of the denervated part persists until regeneration of the sensory fibers According to Smithwick and White regeneration of sensory and sympathetic fibers is complete in about three months after crushing a nerve to the extent of one-quarter inch or in six months after one half inch crushing There is no reason to believe that the unfavorable vasomotor and nutritional changes known to occur in the foot of a normal extremity following section of the same peripheral nerves do not develop in a foot with occlusive arterial disease After degeneration of sensory fibers and until regeneration of sensory and sympathetic fibers occurs other measures of treatment for the improvement of the collateral circulation such as warming the body or an unaffected extremity or lumbar sympathectomy when indicated are ineffectual

The only patients that may require an early major amputation in

thromboangiitis obliterans are those with gangrene extending from the digits into the foot or leg, and the rare acute fulminating cases In patients with slowly progressive gangrene confined to one or more toes, amputation at the phalanx proximal to the level of demarcation is often possible after a period of rest and medical treatment If the gangrenous lesion fails to improve under medical treatment or if it extends, which is usually due to new occlusions of the main arteries amputation of the leg may be necessary An amputation five to seven inches below the knee is preferable to a higher amputation when the local circulation of the leg is adequate for healing of the stump Necrotic lesions of the digits in the upper extremity are rare and seldom require amputation

It is now generally accepted that sympathectomy is the most effective method known for inducing a persistent vasodilation of the collateral circulation of an extremity in occlusive arterial disease In 1925 Brown and Adson [48] confirmed the observation of Royle [49] that an extremity after lumbar ganglionectomy for spastic paralysis was warmer than the contralateral extremity Brown, [4] in 1926, reported the relief of intermittent claudication and rest pain and the more rapid healing of ulcers after lumbar sympathectomy in five cases of thromboangiitis obliterans In a series of one hundred consecutive cases treated by sympathectomy, Adson and Brown [44] reported that the average improvement in intermittent claudication and rest pain was 85 per cent as against 56 per cent under active medical treatment and that the incidence of major amputation was decreased from 14 per cent to 5 per cent if the operation was restricted to patients with a surface temperature in affected digits of 29° C (84° F) after a pre-operative vasodilation test They cautioned against performing the operation in the acute stage of the disease and in cases with extensive gangrene of the foot and recommended sympathectomy in other cases after medical treatment had demonstrated improvement in the relief of rest pain, edema, and the healing of necrotic lesions

The beneficial effects of lumbar sympathectomy were soon confirmed by others In a series of forty two cases Telford and Stopford [50] reported that 60 per cent were free of rest pain, able to walk and in most cases able to work 17 per cent had improvement as regards rest pain and their general condition but little or none in walking or capacity to work and 23 per cent showed little or no improvement In twenty nine cases with intermittent claudication as the only symptom of the disease Ross[51] reported that exercise pain was diminished in nineteen but persisted in ten following lumbar sympathectomy Harris [52] reported

that eighteen of twenty four patients showing a rise in surface temperature of 5° to 6° C in the toes after spinal anesthesia had relief of rest pain healing of ulcers and gangrene, and were able to return to work after lumbar sympathectomy but that there was no improvement in another group showing a pre operative rise in surface temperature of 1° C

The late clinical results of lumbar sympathectomy have now been studied in many different centers It is generally recognized that the operation is not a cure for the disease nor does it prevent the development of new occlusions of the main arteries of the leg or foot There is abundant evidence that lumbar sympathectomy is an effective measure for the improvement of the collateral circulation to the skin and subcutaneous tissues of the foot in occlusive arterial disease if the small arteries are free of structural changes and able to dilate with the release of sympathetic vasoconstrictor tone Lynn and Barcroft [3b] found that the surface skin temperature of the digits remains elevated and the blood flow to the foot increases to about double the normal resting level three months after lumbar sympathectomy If sclerotic changes do not develop in the smaller arteries the increased blood flow, which is more than adequate to meet the metabolic needs of skin and subcutaneous tissue of the foot is probably permanent after lumbar sympathectomy Earlier claims of its value for the relief of intermittent claudication have not been substantiated Experience has shown that one cannot rely on the patient s assessment of the effect of a particular treatment on intermittent claudication and that standardized tests are necessary Shepherd [53] determined the exercise tolerance or claudication index by an ergograph and the calf blood flow by a plethysmograph before and immediately after exercise and then at intervals until the blood flow had returned to the resting level in patients with intermittent claudication before and after lumbar sympathectomy He found no significant increase in the claudication index or in the post exercise calf blood flow after lumbar sympathectomy Hamilton and Wilson [30] confirmed his observations They investigated the effect of different methods of treatment used in patients suffering from intermittent claudication and found that a large majority of patients failed to show any improvement in exercise tolerance as the result of treatment These findings demonstrate the failure of sympathectomy and other methods of treatment to improve to any significant degree the exercise tolerance of patients with intermittent claudication and are consistent with present knowledge of the regulation of blood flow and the metabolic require-

ments of active skeletal muscles In the evaluation of methods of treatment in occlusive arterial disease, too little attention has been paid to the difference in the regulation of blood flow and the metabolic requirements between active skeletal muscles and the skin and subcutaneous tissue of the foot

In thromboangiitis obliterans intermittent claudication is an inevitable result from multiple occlusions of the main arteries of the leg and foot A careful clinical history of the development of intermittent claudication and its severity gives one an indication of the frequency of exacerbations and the duration of stationary or quiescent periods in the course of the disease Rate of progress and the stage of the disease when the patient is first seen have an important bearing on the indications for and results of treatment following sympathectomy

Sympathectomy is not recommended during an exacerbation of the disease in the presence of extensive gangrene of the foot and toes, or in acute fulminating cases If intermittent claudication is the only manifestation of the disease, the limited improvement in exercise tolerance that may result from a sympathectomy does not warrant the operation

After an appropriate period of medical treatment sympathectomy is an effective measure in relieving rest pain partially or completely accelerating the healing of open lesions and improving the cutaneous circulation proximal to an area of gangrene often making possible a minor rather than a major amputation Excision of the second and third lumbar ganglia and the lumbar chain proximal and distal to the ganglia results in a complete sympathetic denervation of the lower extremity from the knee to the foot, except the medial aspects supplied by the saphenous nerve, and is an adequate sympathectomy for the improvement of the circulation in thromboangiitis obliterans The inclusion of the first lumbar ganglion will result in a complete sympathetic denervation from the thigh to the foot but a bilateral excision of this ganglion may result in untoward sexual disturbances which should be avoided

Intermittent claudication with postural color changes in the foot, but without rest pain may be present for months or years depending on the course of the disease and the absence of trauma before the development of major nutritional changes in the digits If coldness of the foot is associated with definite postural color changes lumbar sympathectomy should be considered for the prevention of major nutritional changes in the foot The operation will relieve the coldness and increase the blood flow in the cutaneous circulation As a result the tissues of the relatively ischemic foot become warmer and less susceptible to trauma

Arteriosclerosis

Introduction Arteriosclerosis is a pathological rather than a clinical term and in a broad sense includes all types of arterial lesions leading to thickening and hardening of the arteries It is customary however to exclude from this category such conditions as acute arteritis from obvious bacterial infection syphilitic mesarteritis thromboangiitis obliterans periarteritis nodosa, and temporal arteritis Arteriosclerosis increases in frequency and severity with advancing years After fifty years of age the most common cause of incapacity and ultimately of death is arteriosclerotic disease of the vessels supplying the heart, brain kidneys, or extremities Of itself arteriosclerosis produces no symptoms Clinical manifestations of arteriosclerotic disease develop when the structural changes affect the normal vascular control of the circulation or the normal flow of blood in the sclerotic vessels The clinical diagnosis of arteriosclerotic disease therefore must be based on local or general disturbances of function resulting from impairment of the circulation

Although the sclerotic process may affect all arteries of the body and at times be widespread, it is more often localized to vessels supplying one or more regions of the body such as the heart brain or extremities Arteriosclerosis of a degree to cause impairment of the circulation almost always is a localized process and the clinical diagnosis of generalized arteriosclerosis rarely can be justified by subsequent pathological examination of the arteries The tendency to regard arteriosclerosis as a generalized rather than a localized process and to view arteriosclerosis as merely a manifestation of old age has led the clinician to consider the presence of hardening and thickening of the superficial arteries in individuals past middle life as valuable supporting evidence of arteriosclerotic disease of vessels supplying internal organs of the body such as the heart and brain Further he too often fails to recognize that a special type of sclerosis Monckeberg s sclerosis, not found in vessels supplying the internal organs is a common cause of thickening and hardening of superficial arteries such as the radial As stated by Klotz [4]

We are prone to use the term arteriosclerosis carelessly in applying it to the sclerosis of arteries in different portions of the body as if the lesions were all the same and had both a common manner of development and a common effect on the circulatory system In any attempt to correlate the pathological and clinical findings in arteriosclerotic disease the clinician must recognize that there are different types of

sclerosis, and that the effect of these different lesions on the circulation varies not only with the type of lesion but with the size of the affected artery and the site of the lesion

Types of Sclerosis There are four main types of arteriosclerotic lesions atherosclerosis of the intima, medial sclerosis of Monckeberg, arteriolosclerosis, and senile sclerosis of intima and media It is generally agreed that the first three types are acquired forms of arteriosclerotic disease Concerning the fourth type, there are certain tissue changes that develop during senescence in the arteries as well as in other tissues of the body which may be attributed to the process of aging As these changes may result in hardening and thickening of the arteries, it is well to include them as a type of arteriosclerosis under the term 'senile arteriosclerosis'

Senile Arteriosclerosis The most important change in the arteries caused by the process of aging is a deterioration of their elastic tissues [5] After forty-five years of age the elastic tissue tends to become more brittle and there is a progressive loss in its elasticity With progressive loss of elasticity, the larger arteries increase in length and width and become tortuous (senile ectasia) The normal circumference of the root of the aorta increases from 50 millimeters to 70 millimeters, the thoracic aorta from 40 millimeters to 50 millimeters, and the abdominal aorta from 30 to 40 millimeters [5] In the media there is progressive increase of collagenous connective tissue (medial fibrosis) and an atrophy of muscle fibers with increasing age

These elastic tissue changes are accompanied by a diffuse uniform thickening of the intima from an increase of collagenous fibrous tissue which causes a hardening of the larger arteries This thickening of the intima is not confined to the elastic arteries but is present in the muscular arteries of the extremities, particularly the lower extremities In small muscular arteries such as the branches of the dorsalis pedis, radial and arteries forming the collateral circulation after an acute occlusion of a a larger proximal artery from thrombosis or embolism, this diffuse intimal thickening, a form of endarteritis obliterans, causes a marked narrowing of the lumen and even obliteration of these vessels The diffuse uniform thickening of the intima and the absence of lipoid deposits indicate that it is a process distinct from atherosclerosis, in which the lesions are patchy and contain lipoid material

Structural vascular changes resulting from senile ectasia and senile sclerosis cause no interference with the flow of blood in the large elastic arteries or the larger muscular arteries of the extremities, but

may affect the vascular control of the circulation The most serious effect on the circulation is the loss of elasticity in the aorta which impairs its function as an elastic reservoir Loss of elasticity in the aorta and the other large arteries increases the work of the heart in maintaining an efficient circulation The systolic blood pressure is increased and the reserve power of the heart is reduced correspondingly [6] In the smaller arteries of the extremities diffuse thickening of the intima impairs their response to reflex vasodilation and impedes the blood flow through these vessels

Atherosclerosis (Nodular Endarteritis, Nodular Sclerosis) Atherosclerosis is a nodular type of intimal arteriosclerosis It is found most commonly in the aorta and its main branches in the larger coronary renal and cerebral arteries and in the arteries of the extremities with the exception of the smaller arteries and arterioles The chief anatomical change is a patchy thickening of the intima from an increase in the subendothelial connective tissue and from the deposition of lipoid material Difference of opinion prevails as to the cause and nature of this type of arteriosclerosis Some believe the intimal lesion has its beginning as an inflammatory process and that, at a later stage degeneration or atheroma may develop They refer to this type of arteriosclerosis as nodular endarteritis Others are of the opinion that degeneration of the intima is the primary process and that the accompanying fibrosis is secondary, and use the term atherosclerosis According to Klotz [57] the process may begin either as a primary degeneration of the intima as seen in the form of fatty streaks in the intima or as a primary endarteritis as is found accompanying some of the acute infections of childhood

The earliest lesions are found in children and young adults suffering from acute infections and intoxications and appear as fine yellow streaks or spots in the intima These streaks or spots represent deposits from the blood stream of lipoid material chiefly cholesterol esters in the subendothelial layer or in the musculo elastic layer or in both layers of the intima [58] Associated with this process is a proliferation of the subendothelial connective tissue but no definite relationship exists between the quantity of lipoids and the degree of fibrous thickening in the intima In fatal cases of acute infections in young children Klotz found a primary proliferative lesion in the intima of the coronary and other arteries The proliferation of connective tissue that occurs in this early inflammatory lesion produces a small nodule in the intima which enlarges with a subsequent infection He states these primary

inflammatory nodules represent true types of endarteritis in which when the nodule has become sufficiently large and dense, a secondary process of degeneration involves the deep layer close to the media in fatty and other degeneration'

In young individuals lipoid deposits may be absorbed, leaving little or no damage to the intima apart from the increase of connective tissue which may have developed After middle life, if lipoids are deposited in an intima already showing collagenous tissue thickening from aging the intimal fatty change is no longer reversible In adult life the deposition of lipoids in the depth of the intima is accompanied by a further new formation of connective tissue and produces flat, raised grey nodules of thickened intima which project into the lumen of the artery As the lesion progresses the nodules become thickened and more extensive The newly formed connective tissue undergoes hyaline degeneration and necrosis occurs in the lipoid deposits One or other of these features may dominate the intimal lesion an increase in connective tissue being more prominent in the smaller muscular arteries and fatty changes in the larger elastic arteries Calcium is deposited in the necrotic tissue and in the hyaline connective tissue, forming a calcified plaque When the lesions in the depth of the intima become overloaded with lipids the area softens with the formation of a grumous material In the aorta more particularly, the area of necrosis may extend through the overlying thickened intima forming an atheromatous ulcer At this site a thrombus may form and be the origin of an embolus which finally lodges in one of the peripheral arteries causing an acute occlusion

The nodular thickening is composed of a dense, homogenous, connective tissue which may become calcified The lesion causes a narrowing of the lumen which may be so pronounced as to cause a partial occlusion with or without secondary thrombosis Intimal lesions may extend to the media but atrophy of the media from pressure of the local nodular thickening on the intima is the usual result In the smaller arteries such as the branches of the larger coronary, renal and cerebral arteries and the smaller muscular arteries of the extremities atheromatous changes with softening are uncommon

Etiology Artherosclerosis is found with increasing frequency after forty five years of age but may appear in younger individuals It is not simply a matter of growing old but represents an acquired form of arteriosclerosis There is no agreement as to its underlying causes Advanced lesions more particularly in the coronary arteries, may be

present in the fifth fourth, or even the third decade of life Adlersberg *et al* [9] consider a hereditary disturbance of lipid metabolism one of the conditioning factors in the development of coronary atherosclerosis in younger individuals In some individuals living to a ripe old age the arteries may show no significant signs of atherosclerosis The absence of sclerosis in certain elderly people the early development of advanced lesions in others and the tendency for arteriosclerotic disease to occur in certain families support the suggestion of Osler that an inherited quality of the arteries also exists making one person less and another more susceptible to the development of intimal sclerosis from environmental influences

Alteration in the blood pressure such as the moderate increase in systolic pressure which may be present in atherosclerosis of the aorta is now regarded as the result and not a cause of atherosclerosis There is evidence that essential hypertension (diastolic hypertension) accelerates the development of atherosclerosis The more frequent occurrence of atherosclerosis in certain arteries aorta coronary cerebral the orifices of the intercostal arteries the left coronary as compared to the right coronary, and even in different portions of the same artery such as the abdominal aorta and the thoracic aorta is most likely due to different local anatomical mechanical and hemodynamic factors Alcohol lead and tobacco would not appear to be of etiological importance

When one comes to consider other possible factors responsible for the development of this type of sclerosis no agreement exists as to the cause and nature of the earliest or primary lesion of the intima Local intimal lesions closely simulating the early fatty streaks or spots as well as the older more advanced proliferative and degenerative lesions of the intima in man have been produced in the arteries of rabbits by the feeding of diets rich in cholesterol [60] From his cholesterol feeding experiments in the rabbit and his study of human atherosclerosis Anitschkow [10] has come to the conclusion that a disturbance of cholesterol metabolism is the most important factor in the etiology of human atherosclerosis He states If the insufficiency of the cholesterin metabolism is of a pronounced character it may lead to the development of atherosclerosis even without any other concomitant cause If it is less severe it may have the same consequences provided that it is either of long duration or associated with other predisposing factors Among the latter those of a mechanical nature probably are the most important Other factors that may in some way exert a noxious influence on the arterial wall are those of toxic of infectious toxic and of nervous nature

It is now generally agreed that the intimal lesions in experimental cholesterol atherosclerosis in the rabbit are similar to those found in man. There are certain differences in the localization of the lesions but more significant differences would appear to be that hypercholesterolemia and the accumulation of lipids in the reticulo-endothelial system precede the appearance of the earliest intimal atherosclerotic lesion in the rabbit and not in man. It is well known that the atherosclerotic process advances more rapidly, is more marked, and prone to develop at an earlier age in conditions with an associated hypercholesterolemia such as a familial xanthomatosis, but there is no satisfactory evidence that hypercholesterolemia is essential for the development of atherosclerosis in man. Gardner[61] states 'In man there is no evidence whatever to associate the occurrence of atherosclerosis with the exogenous cholesterol metabolism.' Peters and Van Slyke[6] state 'No general disturbance of lipid metabolism has been demonstrated in atherosclerosis.' Weiss and Minot[63] remark 'It cannot be stated that overnutrition with lipoid and fatty substances plays a role in the production of atherosclerosis in man.'

Lipids are present in atherosclerotic lesions in about the same proportion as in the circulating plasma[64] and it is generally accepted that the lipids in the local intimal lesions are derived for the most part from the circulating plasma and to a very limited extent from the local breakdown of tissue in the intimal lesion. However, the lipid deposits in the intima are local rather than diffuse and the circulating lipids cannot be considered the sole determining factor for their local deposition in the intima. As stated by Duff,[6] the amount and physio chemical state of the lipids in the blood plasma may determine whether an atherosclerotic lesion will occur or not, but such factors cannot influence its localization. It seems evident that a primary alteration in the intima is essential for the local deposition of circulating lipids, resulting in the development of atherosclerosis. The localization, at all ages of lipid deposits in the arch of the aorta and the lower aorta at the bifurcation of the iliac and about the mouths of the intercostal arteries would appear to be dependent upon certain mechanical stresses in these areas. The role of physical stress has been discussed recently by Willis.[86] Aschoff[6] considered the deposits of lipids in the intima as evidence of a local functional deterioration in this tissue due to mechanical stress in the young with a molecular change in the cement substance of the intima associated with the process of aging as an added factor in individuals over forty five years of age. Klotz[5] also considered local lipid deposits as an index

of certain damage imposed upon the tissue of the intima but favored infection rather than wear and tear as a cause of the primary alteration in the intima The studies of Karsner [60] on the coronary arteries afford support to the conception that infections may be a cause of damage to the intima and favor the deposition of lipids Winternitz *et al* [0] are of the opinion that intimal hemorrhages from the intramural circulation are an important factor in the development of atherosclerosis but vascularization of the intima is more often regarded as secondary rather than a primary process Leary [1] considers atherosclerosis a metabolic disease He believes that lipid filled cells (foam cells) invade the sub endothelial layer of the intima as a primary process He states however that stresses determine the sites of localization in the arteries thereby recognizing that a primary change in intima is a determining factor in localization In experimental cholesterol atherosclerosis in the rabbit Duff [2] has shown that the deposition of lipid is preceded by a swelling of the subendothelial ground substance and sometimes by fraying of the intimal elastic lamina It seems clear that a local alteration of the intima precedes the deposition of lipids and constitutes the primary initial lesion in human atherosclerosis and that factors causing a local alteration in the intima play an essential role in the development of atherosclerosis from the deposition of circulating lipids

In recent years Duguid has revived and elaborated the century old view of Rokitansky that atherosclerosis begins with the deposit of fibrin on the internal surface of arteries which becomes incorporated into the intima by organization and by the formation of a new covering of endothelium According to this premise the nodular thickening of the intima in atherosclerosis is the result of surface deposits of fibrin on the intima (mural thrombi) and fatty changes in the intima are a secondary phenomenon As Duguid observed that fibrinous deposits were more readily found at the sites where superficial fatty streaking of the intima is most common it seems evident that the deposition of lipids in the intima is more often primary than secondary to the formation of mural thrombi Duguid believes that nodular intimal thickening from recurrent mural thrombi and not from the primary deposition of lipids in the intima is the common cause of extreme narrowing of the lumen of arteries of the size of the larger coronary arteries and that fibrous thickening of the intima from mural thrombi is the one factor of importance in fatal coronary disease from atherosclerosis Further work is necessary to decide the importance of thrombotic intimal thickening as a cause of narrowing of the lumen in arteries in athero

sclerosis The revival of the thrombosis hypothesis in the pathogenesis of atherosclerosis has led to the suggestion by Fullerton *et al* that alimentary lipemia which they found increased the coagulability of the blood may be a factor in the pathogenesis of thrombosis and of atherosclerosis[43, 44]

In normal individuals the total cholesterol level in the blood is fairly constant for the individual[3] but varies in different normal individuals[74] There is no significant change in the mean value of cholesterol among normals in different age groups[75] In patients suffering from coronary disease, reports of cholesterol levels show that the mean value is higher than in control groups, but there is considerable overlapping in values in the coronary and control groups[?6] In view of this overlapping of values it is evident that hypercholesterolemia is not essential for the development of atherosclerosis in man As further evidence Lande and Sperry found no correlation between the levels of blood cholesterol and the lipid content and the severity of atherosclerosis of the aorta at autopsy And Ahrens and Kunkel[78] report that in four patients with primary biliary cirrhosis skin xanthomatosis and total cholesterol levels over 500 milligrams per cent, and who died and were examined post-mortem the degree of atherosclerosis was no greater than that to be expected at their ages They found that the clarity of high lipid sera in patients with primary biliary cirrhosis and a degree of atherosclerosis commensurate with their age is closely correlated with elevated proportions of serum phospholipids giving a cholesterol phospholipid ratio less than 1 These findings confirmed the observation of Boyd[9] that phospholipids play an important role in maintaining the stability of plasma and lipid emulsions As the cholesterol-phospholipid ratio is more than 1 in patients with essential xanthomatosis and premature atherosclerosis Ahrens and Kunkel concluded that a relationship appears to exist between the fixation of lipids in the intimal cells and increased cholesterol phospholipid ratios This conception is supported by studies in experimental cholesterol atherosclerosis in the rabbit and in coronary artery disease in man Duff and MacMillan[80] found that alloxan diabetes inhibited the development of atherosclerosis despite the presence of a marked hypercholesterolemia This inhibition was associated with a marked elevation of the serum phospholipids that occurred concomitantly with the rise in serum cholesterol Kellner *et al*[81] were able to produce a marked increase in the serum phospholipids and inhibition of the development of atherosclerosis in the rabbit by the intravenous injection of the detergents Tween 80 or Triton A20 In patients

with angina or who had suffered an attack of cardiac infarction different investigators have found an increased cholesterol phospholipid ratio It seems evident that an increased cholesterol phospholipid ratio favors the deposition of lipids in the intima and a decreased ratio tends to prevent it

Recently attention has been directed to the lipoproteins and their relationship to the development of atherosclerosis Gofman *et al* [*] developed an ultracentrifuge technique for the study of giant lipoprotein molecules in the plasma They found that lipoprotein molecules having a Svedberg flotation (Sf) of 1 to 20 and 35 to 100 were present in abnormally high concentrations in patients with cardiac infarction and diabetes mellitus They also showed that Sf 12 20 lipoprotein levels are associated with atherosclerosis independent of their relationship with the serum cholesterol levels In experimental cholesterol atherosclerosis in the rabbit they found that the development of atherosclerosis was related to the concentration of Sf 10-30 class of lipoproteins and not to *the Sf 10 or less or Sf 50 or over*

It has been estimated that 75 per cent of the total cholesterol in the plasma is found in alpha lipoprotein fractions and the remainder in the beta lipoproteins [34] Barr and his associates [84] applied the Cohn microfractionation method number 10 for the separation of proteins in plasma and found that essentially all of the cholesterol and phospholipid of plasma is combined with protein in the form of either alpha or beta lipoprotein They found that the cholesterol phospholipid ratio of the alpha lipoproteins averaged 0 5 while that of the beta lipoproteins averaged more than 1 In patients with cardiac infarction xanthoma tendinosum and diabetes mellitus, they found a tendency to reduction in alpha lipoproteins and a relative and absolute increase in beta lipoproteins They report the interesting finding that these changes may be apparent without hypercholesterolemia or significant elevation of cholesterol phospholipid ratio in the fractionated plasma and may be present in diabetes mellitus before vascular complications of the disease are clinically recognizable They confirmed the observation of Ahrens and Kunkel [8] of a low cholesterol phospholipid ratio in biliary cirrhosis but found a low ratio in both the alpha and beta lipoprotein fractions

Kunkel and Slater [8] have studied the alpha and beta lipoproteins pattern in normal and pathological sera Their findings are in general agreement with those of Barr and associates [84] using chemical separation of blood proteins From the observations reported it seems evident that the phospholipids play a definite role in stabilizing the solution of cholesterol in the plasma the low cholesterol phospholipid ratios in the

alpha lipoproteins increasing the solubility of cholesterol and preventing the deposition of lipids in the intima, and the high cholesterol-phospholipid ratio in the beta lipoproteins decreasing solubility and favoring deposition of lipids

It would appear that hormones play a part in the metabolism and/or distribution of lipids in the plasma It is well known that coronary heart disease is much more common in males than in females In a group of 100 patients under forty years of age with coronary heart disease, White[86] reports ninety-seven males and three females Gofman *et al*[8] found an appreciable increase in the Sf 12-20 lipoproteins in normal males from twenty-five to thirty years of age, which was maintained without significant change to the sixtieth year In normal females they found a slow and steady rise in the Sf 12-20 lipoproteins from the twenty fifth to the sixtieth year when they reached the level of males Barr and associates[9] found no significant differences in the percentage of cholesterol in the alpha and beta lipoproteins respectively in men and women from forty five to sixty-five years of age, but in young individuals between eighteen and thirty-five years of age, the percentage of cholesterol in alpha lipoproteins was 35 per cent in young women and 25 per cent in young men with a corresponding decrease and increase respectively in beta lipo proteins They treated with estrogens eighteen patients who had survived an attack of myocardial infarction and found that the treatment was accompanied by an increase in the percentage of cholesterol in the form of alpha proteins and a corresponding reduction in the percentage of cholesterol in the beta lipoproteins and a tendency towards a reduction in the total cholesterol in the plasma Upon withdrawal of estrogen therapy there was a prompt increase in the concentration of total cholesterol and diminution in the percentage of cholesterol in the form of alpha protein Circulating estrogens would appear to affect the distribution of cholesterol between the alpha and beta lipoproteins and influence the deposition of lipids in the intima Gertler and Garn[44] found a low blood cholesterol level and strikingly low incidence of coronary heart disease in eunuchs

It is often stated that myxedema promotes the development of athero sclerosis but evidence that thyroid deficiency is a predisposing factor in the development of atherosclerosis in man is unconvincing[89] Blumgart *et al*[90] reported the clinical and post-mortem findings in eight patients with rheumatic heart disease or cor pulmonale in whom hypothyroidism or myxedema was present basal metabolic rates of approximately minus 20 per cent with elevated levels of plasma cholesterol were found, they

survived one to thirteen years following surgical total thyroidectomy None of the eight patients showed complete occlusion of any of the coronary arteries and five of the eight showed no narrowing of the coronaries In other arteries the atherosclerotic lesions were similar to those found in similar euthyroid patients It has been shown by Hurxthal[91] and Gilligan *et al*[92] that the concentration of plasma cholesterol bears a reciprocal relationship to the basal metabolic rate and that the administration of thyroid results in a significant decrease in the concentration of plasma cholesterol Proof that the increase in plasma cholesterol is related to the deficiency of the thyroid hormone and not to the low metabolic rate is afforded by a study of the effects of dinitrocresol and dinitrophenol Dodds and Robertson[93] found that the increase in metabolic rate following the administration of dinitrocresol did not alleviate the signs and symptoms of myxedema and Cutting *et al*[94] showed that the administration of dinitrophenol is not accompanied by a corresponding drop in the level of the plasma cholesterol In their studies of the serum lipids in thyroid disease Peters and Man[95] found that the cholesterol phospholipid ratio is not affected by disorders of thyroid function and within the normal range of cholesterol, is the same for patients with normal excessive or deficient thyroid activity varying with the concentration of cholesterol They found that the phospholipids which are stabilizing agents in the serum increase faster than the cholesterol following thyroidectomy and the development of hypothyroidism This finding supports the morphological evidence that the severity of atherosclerosis in hypothyroidism and myxedema is not significantly greater than in euthyroids of the same age group

In animals the thyroid hormone would appear to play a definite role in the development of hypercholesterolemia and experimental athero sclerosis in rabbits Turner[96] found that in rabbits fed a normal diet thyroidectomy increased the level of blood cholesterol 19 per cent but in rabbits with hypercholesterolemia due to cholesterol feeding thyroidectomy was followed by a 137 per cent increase in the cholesterol level He also found that the feeding of thyroid simultaneously with cholesterol was effective in preventing the development of hypercholes terolemia and atherosclerosis of the aorta in rabbits In the dog choles terol feeding alone fails to produce atherosclerosis Steiner and Kendall[97] produced hypercholesterolemia and atherosclerosis lesions in the dog by the administration of thiouracil and the feeding of cholesterol

It is known that the incidence of atherosclerosis of the coronary and peripheral arteries is higher in diabetics than in non diabetics in the

same age group. This higher incidence would seem to depend more on the duration than the severity of the diabetes mellitus. The factors which seem to promote the premature deposition of lipids in the intima of young diabetics and accelerate their deposition in older diabetics have not been determined. In diabetes mellitus the average level of total lipids, cholesterol and phospholipids is higher than normal but no significant variation from normal is present in many diabetics. The lipid pattern is similar to that found in the atherosclerotic non diabetic. It would appear that the metabolic disorder in diabetes mellitus accelerates the deposition of lipids in the intima, for it is generally recognized that the atherosclerotic process advances more rapidly in the untreated and the uncontrolled diabetics. With adequate treatment of the metabolic disorder the lipid pattern returns to normal for the age of the patient. In a group of adult diabetics under adequate treatment for a period of fifteen years, Fletcher and Graham[98] found no undue arterial change in advance of their years. The cause of the greater frequency of coronary atherosclerosis in younger diabetic females than in non diabetic females in the same age group and the high incidence of fatal coronary atherosclerosis among non diabetic soldiers under forty years of age serving in the American Army in World War II[99] remain undetermined. The genetic studies of Adlersberg *et al*[7] on families with xanthoma and unselected cases of premature coronary atherosclerosis suggest that an hereditary fault of lipid metabolism which is transmitted as a Mendelian dominant may be a causal factor.

Medial Sclerosis of Monckeberg. Monckeberg's sclerosis is a primary degeneration of the media in the large and medium-sized muscular arteries of the periphery. It is much less common in the upper than in the lower extremities.[300] The arteries of internal organs are seldom involved. It is found most frequently in the lower two-thirds of the femoral and in the anterior and posterior tibial arteries, less often in the radial and ulnar arteries and much less frequently in the popliteal and brachial arteries.[301] The primary lesion is a fatty degeneration of the muscle fibers with a granular change in the ground substance of the media, followed by the deposition of calcium. The calcium deposited as fine granules in the intercellular substance of the media tends to form rings giving rise to the hard and beaded arteries commonly found in elderly people. In other cases the deposits tend to form plate like masses which may fracture and heal by fibrous union. True bone containing bone marrow has been found in the larger calcareous deposits. Medial

degeneration followed by calcification may occur with or without intimal thickening [5] The development of sclerotic changes in the intima has no direct relation to the antecedent degeneration in the media

Medial calcification is common after middle life and increases in severity with advancing years but it appears at an earlier period in patients suffering from diabetes mellitus hypothyroidism or conditions characterized by hypercalcemia The quality of the arteries functional stresses and intoxications would appear to be the chief determining factors in its development The production of similar lesions in the media of the aorta of rabbits by intravenous injections of adrenalin and other substances such as amyl nitrite digitalis nicotine and diphtheria toxin suggests that intoxications are important factors in the development of degeneration of the media in man

Monckeberg s sclerosis results in a widening rather than a narrowing of the lumen of affected arteries It causes no interference with the flow of blood and probably has little deleterious effect on the control of the circulation Marked medial calcification of the peripheral arteries may be present without any appreciable disturbance of the circulation If local vascular disturbances of the extremities are present in patients showing signs of medial calcification they are due to intimal lesions—atherosclerosis— in the same vessels or to senile arteriosclerosis in their smaller or more distal branches

Arteriolosclerosis (Diffuse Hyperplastic Sclerosis) In arteriolosclerosis the lesion of the intima affects the pre capillary or terminal arterioles and their parent arteries The lesion is most commonly found in the arteries of the parenchyma of the kidney spleen pancreas and liver in the intracerebral branches of the cerebral arteries in the intramuscular branches of the coronaries and in the retinal arteries It is a lesion of the intimate vasculature of internal organs [30] Similar lesions have been found in the arteries supplying skeletal muscles in cases of essential or primary vascular hypertension [303]

In the benign or chronic form of essential hypertension the essential lesion is a thickening of the intima and media in the arterioles and their parent arteries According to Evans [30] the earliest structural change in the arterioles is a hyaline swelling and a proliferation of the endothelial cells of the intima which later undergo fatty changes In the parent artery there is a uniform thickening of the intima from hyaline swelling elastic hyperplasia and proliferation of connective tissue Cellular proliferation is minimal and fatty changes are absent These intimal changes

usually are accompanied by a thickening of the media from hypertrophy of muscle fibers and a hyperplasia of elastic fibers Intimal changes in the arterioles and parent arteries result in narrowing and even obliteration of the lumen of these vessels

In malignant hypertension or in an acute exacerbation of the more common benign form of essential hypertension a more acute reaction develops The essential lesions are an arteriolar necrosis affecting the whole thickness of the vessels and a cellular hyperplasia The walls of the arterioles are swollen and stain a diffuse red with eosin Nuclei have disappeared or are present as nuclear fragments Edema and hemorrhage in or about the affected arterioles are common, at times thrombosis of the adjacent capillaries may result Necrosis of the arterioles is accompanied or followed by thickening of the intima and media from an increase of connective tissue and an endothelial hyperplasia—an endarteritis

Intimal changes in the small arteries of the kidney were observed by Bright in patients with contracted kidneys but Gull and Sutton[304] were the first to call attention to the occurrence of similar changes in the arteries of organs other than the kidney They described them under the title 'arterio capillary fibrosis The presence of these sclerotic changes in association with persistent hypertension and cardiac hypertrophy in patients with contracted kidney led to the belief that both the hypertension and the vascular changes were the result of primary renal disease Later, Allbutt[30] called attention to the fact that persistent hypertension and left ventricular cardiac hypertrophy might be present and the patient die of cardiac insufficiency or apoplexy with little or no sign of renal involvement To define this group of cases he introduced the term hyperpiesia The observations of Allbutt have since been confirmed by others but the condition described by him as hyperpiesia is now more commonly referred to as essential or primary vascular hypertension It is in this condition that arteriolosclerosis is most commonly found and may be present without the larger arteries showing any significant signs of other types of sclerosis

In arteriolosclerosis there would appear to be a causal relationship between the hypertension and the development of structural changes in the arterioles and their parent arteries In consideration of this possible relationship too often no attempt is made to distinguish between patients with an increase in the systolic pressure and a normal or subnormal diastolic pressure and patients with an increase in both the systolic and diastolic pressures When this lack is coupled with failure to differen

tiate different types of arteriosclerosis, confusion is bound to result It has already been pointed out that in both senile sclerosis and athero sclerosis the systolic pressure is normal or more often shows a moderate rise above normal and the diastolic pressure is normal or subnormal further that the increase in systolic pressure is the result and not the cause of the associated arteriosclerosis In essential hypertension on the other hand there is a rise in both the sytolic and diastolic blood pres sures This abnormal rise in both the systolic and diastolic pressures probably is due to increased tonus of the arterioles in the peripheral and splanchnic areas of the arterial system but the cause of the increased tonus is unknown It is thought to be humoral in origin Blood pressure readings taken during the early stages of essential hypertension usually show wide variations from normal to higher definitely abnormal levels but in time the lower limit of both the systolic and diastolic pressures tends to become fixed at a much higher level than normal with tempo rary fluctuations particularly in the systolic pressure above this level In the stage of persistent hypertension, the earliest period in which an absolute diagnosis of hypertension can be made the lower limit of the systolic pressure is 180 mm Hg and that of the diastolic pressure 100 mm Hg

In the early labile phase of essential hypertension structural changes in the arterioles and their parent arteries are minimal or absent It is in the stage of sustained high diastolic pressure that one finds the arteriolo sclerotic changes of benign hypertension the acute vascular lesions of malignant hypertension and the associated left ventricular hypertrophy It is now generally agreed that the increase in blood pressure in essential hypertension precedes the development of structural changes in the arterioles This view first advanced by Allbutt is supported by findings in experimental hypertension Goldblatt[3 6] found that when the blood pressure was raised and maintained at a moderately high level by a clamp on the renal artery of dogs arteriolosclerotic changes closely simulating those found in the benign form of essential hypertension developed but if a very high blood pressure was produced by further tightening the clamp arteriolar necrosis developed[307] Using methods essentially similar to those used by Goldblatt Wilson and Pickering[308] found in rabbits that a rapidly developing severe hypertension caused arteriolar necrosis and in many instances an associated cellular intimal thickening—lesions similar to those found in malignant hypertension They were of the opinion that the cellular intimal thickening may be produced by organi

zation of the acute fibrinoid necrosis In animals with moderate hyper tension, no acute lesions were found Pickering and Prinzmetal[309] found the heart to be hypertrophied in rabbits with hypertension, and there seemed to be a relationship between the degree of hypertrophy and the degree of hypertension It seems clear that the factor or factors primarily responsible for the persistent high diastolic pressure and the sudden fluctuations that may occur from time to time above this abnormal high level in essential hypertension are the cause of the acute and chronic structural changes in the arterioles and their parent arteries in this disease

An almost constant finding in essential hypertension, apart from the early labile phase is left ventricular hypertrophy [30] In the course of the disease grave signs and symptoms may develop, and these are due most often to cardiac insufficiency or cerebral hemorrhage and less often to renal insufficiency In young individuals dying of cardiac insufficiency the result of essential hypertension, the left ventricle is found to be markedly hypertrophied, the myocardium, apart from the size of the muscle fibers may appear normal or show small areas of red necrosis or fibrosis but the main branches of the coronary arteries show no signs of sclerosis It is evident from these observations that sclerosis of the main branches of the coronaries is not an essential factor in the development of cardiac hypertrophy and the subsequent cardiac insufficiency in essential hypertension It seems clear that the persistently high pressure particularly the high diastolic pressure is the cause of the left ventricular hypertrophy and the chief factor in the later development of coronary insufficiency It is well known that cerebral hemorrhage is the usual cause of apoplexy in cases of essential hypertension and that thrombosis is the usual cause in the nonhypertensive with atherosclerosis of the cerebral arteries In essential hypertension not complicated by athero sclerosis of the main cerebral arteries, the hemorrhage in apoplexy may arise from the smallest intracerebral arteries and capillaries[310] due to a functional disturbance, possibly spasm, of these vessels [311, 31] A similar mechanism probably is responsible for the development of hemorrhages and exudates in the fundus oculi in malignant hypertension In the be nign form of essential hypertension, arteriolosclerotic changes in the kidney are seldom the cause of death from renal insufficiency On the other hand the acute arteriolar lesions of malignant hypertension are constant findings in the kidney and result in progressive impairment of renal function

Diagnosis of Peripheral Arteriosclerotic Disease Arteriosclerotic le sions of themselves produce no symptoms Signs of arteriosclerosis may

be detected in the larger peripheral arteries by inspection and palpation but the information gained is of limited value in the diagnosis of arterio sclerotic disease as a cause of local or general circulatory disturbances Signs and symptoms of circulatory disturbance due to arteriosclerosis develop when sclerotic lesions cause local interference with the flow of blood in the arteries and the supply of blood becomes inadequate to meet the needs of the tissues The clinical diagnosis of arteriosclerotic lesions therefore must be based on clinical findings which result from a deficient supply of blood As there are four main types of arteriosclerosis which differ in their site of origin and distribution and in their effect on the circulation one should attempt to determine the site of the sclerotic lesion or lesions primarily responsible for the disturbances and also the type or types of arteriosclerosis producing them

In *senile arteriosclerosis* the aorta and the larger peripheral arteries are widened and lengthened from loss of elasticity and as a result become tortuous The presence of a tortuous brachial artery is supporting evi dence of similar changes in the aorta which may be confirmed by ex amination of the ascending aorta under the X ray The systolic blood pressure may show a moderate increase to about 160 mm Hg but the diastolic pressure is normal or subnormal The reserve power of the heart is decreased [8] and as a result the exercise tolerance is also de creased but no significant enlargement of the heart is present In fact the heart may be smaller than normal Loss of elasticity in the aorta, its main branches and the larger muscular arteries of the extremities may lead to a very slow but gradual impairment of the general circulation through its effect on the vascular control of the circulation and on the work of the heart In the smaller muscular arteries of the extremities diffuse rather than localized intimal thickening causes a narrowing of the lumen or even obliteration of these vessels and thereby contributes to the impairment of the local circulation caused by atherosclerosis of the larger proximal arteries

Monckeberg s sclerosis affects the media of the large and medium sized muscular arteries of the extremities chiefly the lower It is respon sible for the hard beaded thickening of the radial and proximal portions of the tibial arteries commonly found in elderly individuals and in younger persons with uncontrolled diabetes mellitus Although the palpable peripheral arteries may be rigid contraction of these vessels impaired and marked calcification of the media demonstrated in an X ray plate of the extremities no appreciable disturbance in the local or general circulation may be present Medial sclerosis is not a cause of

obliterative vascular disease It very rarely affects arteries supplying the internal organs and its presence in the peripheral arteries is of no value in the diagnosis of sclerotic disease of arteries like the coronary and cerebral

Atherosclerosis is not only the most common cause of circulatory disturbances of vascular origin but is the chief, if not the sole, primary cause of local circulatory disturbances due to arteriosclerotic disease On pathological examination of the arteries minimal intimal lesions may be widespread but advanced lesions usually are localized to the aorta and to the muscular arteries supplying certain organs or regions of the body Atherosclerosis of the muscular arteries of a degree to cause significant signs and symptoms is almost always localized in the main branches of the coronaries, in the cerebral and renal arteries, or in arteries of the lower extremities varying in size from the popliteal to the dorsalis pedis Muscular arteries supplying other organs of the body and the upper extremities may be affected by atherosclerosis but vascular disturbances from this cause are uncommon

Signs and symptoms resulting from atherosclerosis develop when the blood flow through the sclerosed artery becomes inadequate to meet the needs of the tissues supplied by the affected vessel It is for this reason that extra exertion may mark the onset of early signs and symptoms The sudden onset of grave signs and symptoms usually is due to the development of thrombosis at the site of an atherosclerotic lesion for atherosclerosis is the one type of arteriosclerosis that commonly predisposes to thrombosis The clinical manifestations in atherosclerosis chiefly depend on the site of the lesion or lesions and on the rate of their development Stenosis in the main branches of the coronaries from atherosclerosis is the chief cause of angina pectoris and alone, but more often accompanied by thrombosis, is the important cause of cardiac infarction It is also a cause of chronic myocardial disease with the development of auricular fibrillation and cardiac insufficiency in the later stage of the process A moderate hypertrophy of the heart usually is present but is much less marked than that found in essential hypertension In cases of atherosclerosis not complicated by essential hypertension or other forms of diastolic hypertension the blood pressure as in senile arteriosclerosis, often shows a moderate increase in systolic pressure but no significant change from normal in diastolic pressure The systolic hypertension is an unlikely factor in the causation of the cardiac hypertrophy associated with atherosclerosis of the coronary The probable primary cause is the deficient blood supply to the myo

cardium resulting from stenosis of the coronary arteries Stenosis of the cerebral arteries from atherosclerosis may be the cause of a slow impairment of cerebral function from deficient blood supply, or even acute disturbances may develop due to accompanying thrombosis or to rupture of sclerosed vessels

After forty five years of age essential hypertension is the most common cause of cardiac enlargement and a frequent cause of cardiac insufficiency It is not a cause of angina pectoris but may be an inciting factor in the development of both angina pectoris and coronary thrombosis from atherosclerosis In essential hypertension hemorrhage rather than thrombosis of a sclerosed cerebral artery is the cause of apoplexy The association of high blood pressure with atherosclerosis of the cerebral arteries increases the danger of rupture of the diseased vessels Sclerosis of the main branches of the renal artery is a rare cause of renal insufficiency but arteriolosclerosis of the arteries of the parenchyma of the kidney is the cause of renal insufficiency in over o per cent of cases of essential hypertension [313]

In the diagnosis of atherosclerosis as a possible cause of cardiac cerebral or renal disturbance one should bear in mind that essential hypertension often is an associated finding and may prove an important contributing cause of the clinical manifestations present With the development of cardiac insufficiency, auricular fibrillation or coronary thrombosis the blood pressure particularly the systolic pressure may fall and make the diagnosis of pre existing essential hypertension a difficult problem Usually however, the abnormally high diastolic pressure is maintained at a level above 100 mm Hg and this finding, coupled with the presence of cardiac enlargement and often characteristic changes in the fundus oculi serves to establish the diagnosis of a pre existing hypertension

For further details of arteriosclerotic diseases of special organs or systems the reader is referred to sections dealing with diseases of special organs or systems elsewhere in Oxford Medicine

Arteriosclerosis of the Peripheral Arteries Arterial disturbances of sclerotic origin are common in the lower extremity as compared to the upper All types of arteriosclerosis are to be found in the arteries of the extremities but atherosclerosis is the type primarily responsible for the more severe peripheral vascular disturbances from arteriosclerotic disease They result from an interference of blood flow caused by multiple stenoses from atherosclerosis occurring in vessels varying in size from the popliteal to the proximal part of the dorsalis pedis After the

sixth decade in life the diffuse collagenous intimal thickening from senile arteriosclerosis in the smaller arteries supplying the skin and adjacent tissues impairs vasodilatation and causes a narrowing of the lumen or even obliteration of these vessels This accounts for the poorer collateral circulation developing in older individuals after an acute arterial occlusion than in younger individuals suffering from vascular occlusion in thromboangiitis obliterans[313] The slow and progressive diminution in the blood supply to the skin from diffuse intimal thickening of the small arteries would appear to be the chief cause of the atrophy of the skin commonly found in elderly people In association with atherosclerosis of the larger more proximal arteries, diffuse intimal thickening of their smaller branches is an important contributing factor in the development of major nutritional disturbances in the feet Monckeberg's sclerosis is not a cause of local vascular disorders from occlusion Essential hypertension and arteriolosclerosis play little part in the development of peripheral vascular disturbances

Arteriosclerosis is the most common cause of obliterative vascular disease of the extremities The general character of the clinical manifestations is similar to that found in thromboangiitis obliterans, the other common cause of obliterative vascular disease of the extremities Numbness and tingling a burning sensation in the toes chiefly the great toe, or coldness of the feet are early complaints Early symptoms first appearing with extra exertion are a sense of heaviness weakness or tiredness of the legs or an aching pain in the calf, front of the leg, or foot These symptoms which appear with exertion and are relieved by rest usually precede the development of the distressing pain of intermittent claudication which is a much less frequent complaint in arteriosclerotic disease than in thromboangiitis obliterans This probably is due to the fact that individuals with arteriosclerotic disease belong to an older age group and may suffer from the effects of atherosclerosis of the coronary or cerebral arteries or from other disorders which prevent them from taking enough exercise to produce distressing pain Muscle cramps at night are not uncommon

On physical examination the foot and lower part of the leg usually are colder than normal even though the patient has made no complaint of coldness Pulsation usually is diminished and may be absent in the dorsalis pedis the posterior tibial or in both or less often in the popliteal The skin of the foot loses its elasticity and becomes dry thin and shiny—atrophy of the skin The toenails are opaque, thickened and deformed rather than pink and thin Calluses are common Postural color

changes in the toes may be present These are the prodromal symptoms and signs of an inadequate circulation in the leg and foot which result from the slow but progressive development of multiple stenoses in the popliteal and the larger arteries of the legs and of obliterative endarteritis of the small arteries of the foot At this stage of the process of gradual arterial occlusion trauma to the toes thrombosis of a sclerosed popliteal tibial or peroneal artery or failure of the general circulation results in the development of the more obvious and serious manifestations of an inadequate circulation of the leg foot or toes Thrombosis of a stenosed popliteal or tibial artery may result in a sudden aggravation of pre existing signs and symptoms or in the appearance of major nutritional disturbances in the toes and foot Gangrene may develop it may be dry or moist depending upon the duration and degree of occlusion from sclerosis in the large and small arteries of the extremity and upon the extent of the collateral circulation at the time of the thrombosis If prodromal signs and symptoms of slow development have been present for a long period before the complete occlusion there is less fluid in the tissues and a dry rather than a moist gangrene is likely to develop The dry form is the one most often found in elderly patients Massive gangrene of the foot and lower leg usually is due to an acute occlusion of the femoral artery from embolism or thrombosis

In dry gangrene the affected part is cold pale and dry Later it becomes brownish black in color shrunken and hard Severe rest pain usually is present Along the line of demarcation between the mummified part and the more healthy tissues a fissure may form followed by the development of granulation tissue If infection does not develop in the gangrenous area after some months the dead tissue may separate from the bone leaving it exposed In moist gangrene the area is cold cyanosed and swollen bullae form and the epidermis is easily rubbed off leaving a raw moist surface Later the part may become greenish black in color The greater amount of fluid in the tissues at the time of the thrombosis favors the development of infection which is followed by liquefaction of the gangrenous area Unless infection is controlled promptly by the parenteral administration of penicillin or the affected part is amputated the patient may die of toxemia

Although the primary cause of major nutritional disturbances in the toes is partial occlusion of the larger arteries in the leg and foot from atherosclerosis and of the smaller arteries of the food and toes from senile arteriosclerosis the common inciting cause is trauma It may be caused by exposure to cold mild infections around the toenails me

chanical injury to the tissues from crushing, pressure of ill fitting shoes, and minor abrasions from paring of corns, calluses, or toenails, or by therapeutic procedures on the toes[314] In the non-diabetic a minor abrasion is slow to heal, often leaving an indolent ulcer, but the danger of serious infection is slight Trauma without abrasion of the skin may result in dry gangrene of the part or the whole of one or more toes Rest pain, which often is very distressing usually accompanies these major nutritional disturbances In a diabetic, particularly the inadequately treated diabetic whose tissues are susceptible to infection, similar injuries are almost always followed by infection which tends to spread from the local area to adjacent tissues along tendon sheaths and lymphatics The resultant cellulitis may terminate in a poorly demarcated moist gangrene Rest pain is uncommon in the diabetic

Diagnosis The diagnosis of arteriosclerosis as a cause of organic or obliterative vascular disease of the lower extremity is not a difficult problem An accurate diagnosis can be made in almost all cases by a careful history and complete physical examination The first essential is an appreciation by the examiner of the signs and symptoms of a deficient blood flow in the leg and foot

Arteriosclerotic disease of the extremities is bilateral, but clinical manifestations almost always appear first in one limb and often are confined to one side They are much more common in the lower than in the upper extremity If the body is warm, absence of pulsation in the posterior tibial or dorsalis pedis artery is the most important sign of deficient blood flow in the larger arteries of the leg Important prodromal signs and symptoms are coldness of the foot and leg and weakness or an aching pain in the leg after exertion

Atrophy of the skin of the foot in the non diabetic and the elderly diabetic is supporting evidence of long-standing impairment of the peripheral circulation from arteriosclerotic disease As arteriosclerosis develops more rapidly and at an earlier age in the diabetic, this sign is absent in younger diabetics with arteriosclerotic disease Major nutritional disturbances in the toes are signs of advanced obliterative arterial disease, and trauma is the important inciting cause They may be present in the late stages of Raynaud's disease but the common causes are peripheral arteriosclerosis and thromboangiitis obliterans Gangrene results from complete vascular occlusion Capillary thrombosis is the usual cause of small superficial areas of gangrene in the toes If one or more toes are affected complete occlusion of the smaller arteries supplying them from obliterative endarteritis with or without thrombosis,

is responsible If the area of gangrene involves the foot or leg and foot recent occlusion from thrombosis or embolism of the popliteal femoral or atherosclerotic main arteries of the leg is the likely cause In their injection and dissection studies of the main arteries of the leg in sixty six leg amputations Wessler and Schlesinger[315] *found two or more of the* four main arteries—popliteal anterior and posterior tibial and peroneal —occluded usually at more than one point, with an average of eleven *sites of occlusion per leg* The posterior tibial was invariably occluded and the popliteal in 38 per cent Pulsation of the femoral arteries was present in 94 per cent of cases Recent thrombi causing complete occlusion were present in about one half of the amputated extremities, and in 25 per cent the recent thrombi were multiple

The presence of calcification of the peripheral arteries may be demonstrated by roentgenograms but this method of examination is of little or no value in the clinical diagnosis of arteriosclerotic disease as a cause of peripheral vascular disturbances Arteriography is a valuable aid in the investigation of arterial disturbances of the extremities As a routine diagnostic method it is unnecessary and is not to be recommended

The essential points in the differential diagnosis of peripheral arterial disorders have been discussed under Raynaud s disease and thromboangiitis obliterans

Treatment There is no known method of treatment for the prevention of arteriosclerosis Based on the contention that hypercholesterolemia is a factor in the premature and more rapid development of atherosclerosis in diabetes mellitus the suggestion has been made that a high carbohydrate—low fat diet prevents[316] or delays[317] the development of atherosclerosis in the diabetic patient As it has been clearly shown that no recognizable relationship exists between the blood cholesterol level and the amount of fat in the diet[318, 319, 320, 298] and that a fall in blood cholesterol during the treatment of the disease occurs independently of the carbohydrate-fat balance of the diet[320, 298] any evi*dence of prevention or delay in the development of atherosclerosis must* be ascribed to the adequate control of the diabetes rather than to the type of diet used in treatment There is no sound reason for believing that a diet low in fat or cholesterol will prevent or delay the development of atherosclerosis The prevention of atherosclerosis would appear to depend upon better control of factors causing the primary injury of the intima and the discovery of factors that may inhibit the deposition of lipoid material in the intima Any success attained from new

knowledge in the prevention of atherosclerosis in younger individuals may prove to have a favorable effect in retarding the development of the diffuse intimal thickening associated with the process of aging. Although there is no method of treatment for the prevention of atherosclerosis, much can be accomplished in the prevention of major nutritional disturbances in the extremities caused by arteriosclerosis. If the examination of the arteries of the lower extremities becomes an integral part of the routine examination of patients, fewer will later present themselves for the treatment of truly disabling vascular disorders of the feet.

The management of cases of obliterative vascular disease from arteriosclerosis follows the general plan of treatment outlined for thromboangiitis obliterans. All patients presenting the early symptoms and signs of the former should be cautioned against the danger of trauma to the skin of the feet. The danger of exposure to cold and the importance of keeping the body as well as the feet warm should be stressed. The cessation of smoking is advisable but of lesser importance than in the treatment of thromboangiitis obliterans. If more severe disturbances have developed, such as an abrasion of the skin, a mild infection around the nails, an indolent ulcer, or an area of superficial gangrene, the patient should rest in bed in a warm environment with the affected extremity under a cradle heated by electric bulbs to a temperature of 32° C (90° F). Hot water bottles should not be applied to the extremity. Reflex vasodilatation or oral Priscoline are worthy of trial as a temporary adjunct to general medical treatment of rest pain and minor open lesions. Mild infections should be treated by moist compresses of boracic acid or Dakin's solution 1:12 or 1:6. Strong antiseptics should be avoided. More severe infections should be treated by intramuscular injections of penicillin. Acetylsalicylic acid, phenacetin and codeine are given to relieve rest pain and a barbiturate at bedtime to induce sleep if necessary.

Medical treatment, except in cases of extensive gangrene, should be continued until superficial ulcers heal and a line of demarcation of gangrenous digits is established or open lesions fail to improve. At this stage in treatment lumbar sympathectomy should be considered for the relief of persisting rest pain and for the improvement of the deficient circulation in the skin and subcutaneous tissue of the affected foot. As arteriosclerotic vascular disease, in contrast to thromboangiitis obliterans, develops in patients past middle life, intimal thickening of varying degree is present in the small arteries in addition to a partial or com

plete occlusion of one or more of the main arteries of the leg and only too often prevents maximal vasodilatation of the cutaneous vessels following sympathectomy Preoperative tests are therefore important before sympathectomy is recommended If the surface skin temperature rises promptly to 28° C (83 F) or higher after a paravertebral block of the lumbar sympathetic ganglia or spinal anesthesia an effective vasodilation from sympathectomy may be predicted If the rise in skin temperature is slow and the maximum level below 28 C little or no improvement in the circulation may result from the operation

In carefully selected cases sympathectomy results in the relief of rest pain coldness and persistent cyanosis of the feet and the more rapid healing of superficial ulcers and minor gangrene of one or more toes A slight improvement in walking distance may follow sympathectomy but the operation cannot be recommended for the sole relief of intermittent claudication If the patient's general condition is poor and operation contraindicated Haxton[3 1] recommends injection of the lumbar ganglia with a 6 to 10 per cent aqueous phenol solution which produces a lasting sympathetic interruption He reports favorable results but states that this method of treatment should be employed only by those who have had much experience with paravertebral injection of the sympathetic chain

In the treatment of patients with extensive gangrene or severe infection of the toes or feet it is important to distinguish between cases of arteriosclerosis with diabetes and those without diabetes In the non diabetic severe infections are uncommon and gangrene except in cases where it develops rapidly as a massive gangrene following a recent occlusion of the main arteries of the leg is a slow process and usually manifests itself after sixty years of age as a late development in the process of gradual occlusion of the main arteries of the leg from atherosclerosis and of the smaller arteries of the foot from diffuse intimal sclerosis Atrophy of the skin is present and pulsation in the dorsalis pedis and posterior tibial arteries is diminished or absent The gangrene is of the dry form and trauma is the common precipitating factor If the gangrene involves one or more toes and part of the foot a Gritti Stokes amputation is the operation of choice[3] Penicillin should be administered before and after operation

In the diabetic and particularly in the uncontrolled diabetic with diminished circulation in the feet and toes the development of serious infection following even mild trauma to the toes is always a real danger and its control of paramount importance in treatment A superficial abra

sion of the toe often is followed by a local necrosis, or the area becomes red and swollen and later gangrene develops If not treated promptly infection soon spreads to adjacent tissues Treatment consists of the prompt control of the diabetes by diet and insulin, control of the infection by the parenteral administration of penicillin, and treatment of the local lesion by rest moist compresses of Dakin's solution, and if necessary free drainage by incision with minimal damage to the affected tissues In most cases such treatment is followed by arrest of the infection and healing of the local lesion or by definite localization of a gangrenous area which permits a safer amputation and more prompt healing of the stump The site of amputation depends upon the state of the circulation in the foot and leg and the extent of the gangrenous area If the foot is warm and the treated lesions localized to one or two toes, a local amputation may be performed The control of infection by penicillin has made minor amputations possible in a larger percentage of cases[8 3] With coldness of the foot and gangrene of one or more toes and part of the foot a higher amputation is indicated In patients with a fulminating infection of the foot and ankle, an immediate guillotine amputation below the knee may be necessary

A deep infection with osteomyelitis, may develop in elderly diabetics and non-diabetics under a callus on the sole of the foot or under an infected corn These lesions, which can be prevented by careful attention to corns, calluses and toe-nails, cause little or no discomfort in the beginning but may result in severe local and systemic disturbances from infection Early recognition and prompt treatment are therefore necessary

Occlusion of Large Arteries

Arterial occlusion from embolism or thrombosis occurs most commonly in the smaller systemic arteries but is not a rare occurrence at the bifurcation of the aorta in the common iliac, external iliac, femoral and popliteal arteries, or the subclavian, axillary, and brachial in the upper extremity Arterial occlusion from embolism or thrombosis may occur in the ulnar and radial of the upper extremity but thrombotic occlusions are common in the main arteries of the leg distal to the popliteal Occlusion of the radial or ulnar arteries rarely if ever causes any symptoms In the leg the clinical manifestations of acute occlusion appear as a sudden increase in the severity of pre-existing signs and symptoms of chronic occlusive vascular disease There is no evidence

that an acute occlusion of a normal posterior or anterior tibial artery in the leg causes any symptoms This discussion is confined to occlusions of large arteries

Embolic Occlusion The most common source of emboli causing occlusion of the large systemic arteries is a mural thrombus in the left auricle or left ventricle Thrombus formation in the left auricle occurs in rheumatic heart disease with mitral stenosis complicated by auricular fibrillation and in arteriosclerotic heart disease and hypertensive heart disease with the same complication In approximately 75 per cent of cases of acute embolic occlusion of the aorta, iliac femoral or popliteal arteries, auricular fibrillation is present[3,4] In the left ventricle the mural thrombus forms over an area of cardiac infarction Less common sites of origin of emboli are vegetations on the mitral or aortic valves in subacute bacterial endocarditis or fragments of a thrombus developing in an aortic aneurysm or on an atheromatous plaque in the aorta Very rarely an embolus may arise from a thrombosed systemic vein and reach the aorta through a patent foramen ovale—a paradoxical embolism In our series of 150 cases [4] the sites of lodgment of emboli were as follows subclavian 1 case axillary 3 per cent brachial 10 per cent, aorta (bifurcation), 9 per cent, iliac 9 per cent femoral 4 per cent and popliteal 26 per cent These findings are in general agreement with those reported by others[325 8 6(a)(b) 3 378]

Embolic occlusion of one of the large arteries resulting in ischemia of the lower extremity usually presents a characteristic clinical picture The most common initial complaint is pain which occurs in about 65 per cent of cases[4] The next most common complaints are numbness and coldness of the extremity Haimovici[3,6] noted a sudden onset of signs and symptoms in 81 per cent of cases of acute embolic occlusion, of which 59 5 per cent had sudden pain and 21 5 per cent had sudden numbness and coldness A progressive onset with gradually developing pain and/or numbness and coldness was present in 11 7 per cent of cases The initial pain which is usually severe may be at the level of the occlusion or distal to it in the foot calf, or thigh if the patient has been moving the limb at or just prior to the onset of the occlusion Pain at the level of an occlusion is of short duration and occurs in about 50 per cent of embolic occlusions of the upper femoral and arteries above Poupart's ligament[3,4] It is a sudden sharp pain localized to the loin the lower abdomen, or the groin depending on the site of the occlusion and may shift from loin to groin with the descent of the embolus from the bifurcation of the aorta to the femoral Owing to the short dura

sion of the toe often is followed by a local necrosis, or the area becomes red and swollen and later gangrene develops. If not treated promptly infection soon spreads to adjacent tissues. Treatment consists of the prompt control of the diabetes by diet and insulin, control of the infection by the parenteral administration of penicillin, and treatment of the local lesion by rest, moist compresses of Dakin's solution, and if necessary, free drainage by incision with minimal damage to the affected tissues. In most cases such treatment is followed by arrest of the infection and healing of the local lesion or by definite localization of a gangrenous area which permits a safer amputation and more prompt healing of the stump. The site of amputation depends upon the state of the circulation in the foot and leg and the extent of the gangrenous area. If the foot is warm and the treated lesions localized to one or two toes, a local amputation may be performed. The control of infection by penicillin has made minor amputations possible in a larger percentage of cases.[33] With coldness of the foot and gangrene of one or more toes and part of the foot, a higher amputation is indicated. In patients with a fulminating infection of the foot and ankle, an immediate guillotine amputation below the knee may be necessary.

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tender After about six hours of ischemia they are firm tender, and painful on passive movement With more prolonged ischemia the muscle becomes soft and slightly tender on pressure and passive movement is easily performed gangrene is supervening and recovery is impossible If there is an adequate return of blood flow in the first few hours after an occlusion numbness coldness and pain lessen and disappear Recovery of the pre existing function of the limb may be complete In other cases there is an early and significant improvement in color skin temperature and the sensory and motor disturbances in the limb but recovery is incomplete The common complaints are rest pain of varying severity the pain of intermittent claudication on exercise and pain from ischemic neuritis The clinical manifestations are similar to those found in cases of chronic occlusive arterial disease Distension of superficial veins which may be a later manifestation is an indication of a secondary venous thrombosis

With the exception of the initial brief pain at the level of the occlusion and the later tenderness localized to the site of the occlusion the clinical manifestations of acute embolic occlusion develop distal to the occlusion and are due to the impairment of the circulation in the affected part of the extremity or in other words to ischemia The diminished blood flow is the cause of the coldness present Lewis and his associates[370] have reproduced the sensory and motor disturbances of acute arterial occlusion by arresting the circulation in a main artery in man and have studied their order of appearance and distribution They have shown that, after arrest of the circulation numbness begins to develop in about fifteen minutes to be followed soon by a loss of sense of touch and in about twenty five minutes by weakness and paralysis of muscles in the distal part of the extremity These disturbances resulting from ischemia of the nerves begin in the distal part and extend upwards—centripetal paralysis With a return of the circulation Lewis and his associates observed that sensory and motor disturbances disappeared from above downwards preceded by a sensation of 'pins and needles or tingling in the distal part of the extremity They have shown that this sensation is due to a returning blood supply to ischemic nerve fibers In acute arterial occlusion the development of tingling is an early sign of a returning circulation in an ischemic part

No general agreement obtains as to the cause of the initial pain and the mechanism of its production in acute embolic occlusion The pain may be present at two different sites one at the level of the occlusion and the other distal to it In 1910 Welch[331] suggested that the most

tion of this initial pain at the level of an occlusion, it is often overlooked or not differentiated from the pain developing distal to the site of the occlusion A diffuse aching pain localized distal to the occlusion may precede coincide with or follow the development of numbness and coldness and is present at some stage in all cases of acute embolic occlusion The sudden development of pain or numbness and coldness in an extremity should suggest acute embolic occlusion as a likely cause and prompt an examination of the main arteries of the limb for the presence or absence of pulsations

On physical examination the ischemic limb is pale, waxy white or shows a blotchy cyanosis the limb is cold, arterial pulsations are absent below the site of complete occlusion, and the superficial veins emptied by digital pressure fail to refill from below Sensory and motor disturbances commence distally and spread proximally [3 9] In the distal part of the limb cutaneous sensation and the power of muscular contraction are impaired or lost In acute occlusion of the femoral artery, voluntary movement of the toes and ankle is lost but is present in the knee though impaired The area of coldness extends up the limb to a point a hand s breadth or more below the site of the occlusion which is usually the first bifurcation of a main artery above the area of coldness Branches of the main artery proximal to the occlusion provide a circulation which is adequate for the basal needs of the tissues immediately below the occlusion, maintaining the temperature of the skin at a fairly normal level After twenty-four hours, tenderness over the site of the occlusion is present

The later clinical manifestations in the affected limb depend chiefly on the adequacy of the blood supply and the rapidity with which it is restored to the ischemic limb As stated by Richards,[330] cases of acute embolic occlusion may follow one of four courses (1) the patient dies soon after the episode from the combined effects of the embolism and the primary disease, (2) the patient survives but the affected limb becomes gangrenous and has to be amputated, (3) the limb is preserved but there is some persistent loss of function (4) complete recovery occurs If the motor and sensory effects of ischemia are severe and no significant improvement develops in the first twelve to twenty-four hours after an occlusion the ischemic part becomes congested, cyanosed and swollen collapsed veins become full of blood and gangrene develops Richards[330] has called attention to a series of changes in ischemic muscles and stressed their importance in prognosis At the onset of paralysis the muscles are normal in consistency, but

inadequate collateral circulation is not the cause of the initial sharp pain at the level of an embolic occlusion In such patients complaining of pain on exercise relieved by rest, the proximal pain is felt in the thigh less often in the buttocks, and not in the loin front of abdomen, or groin As to the other causes suggested for this initial sharp pain—distension of the artery by the embolism and arterial spasm—recent studies indicate that spasm is not a cause of vascular pain in large arteries In traumatic arterial spasm of a large artery constriction of the artery may be more marked than in acute embolic occlusion yet pain at the origin of the spasm is an unusual clinical manifestation It seems evident that sympathetic vasoconstrictor fibers are not concerned in the production of spasm of large arteries for spasm of the femoral artery may develop at operation under spinal anesthesia and traumatic arterial spasm is not relieved by periarterial injection of procaine periarterial stripping of the nerve plexus or the injection of the sympathetic ganglia supplying the affected part [334] These observations have been confirmed by Kinmonth and Simone[98] and Kinmonth[99] in their investigations of the cause of spasm of large arteries They found that direct electric stimuli produced no contraction of the upper third of the femoral artery in the rabbit and in man but the same stimulus applied to arteries farther down the limb which are supplied by sympathetic vasoconstrictor fibers from the peripheral nerves caused a definite contraction Their investigations revealed no evidence of a vasoconstrictor nerve supply to the upper third of the femoral or proximal large arteries of the trunk yet these arteries will go into spasm if subjected to mechanical trauma [99] Wilde[335] has shown by microdissection that the nerves to the upper femoral are purely sensory but sympathetic vasoconstrictor fibers are distributed to collateral branches of the upper femoral and to the lower femoral and its branches as shown by Woollard [3] From these observations it would appear that irritation of sensory nerves by sudden distension of the artery by an embolism, as first suggested by Welch [331] is a more likely cause than spasm of the initial sharp pain at the site of lodgment of an embolus in a large artery

In embolic occlusions of the upper femoral or a more proximal artery, the patient may complain of an early severe pain localized to the calf or foot As pointed out by Lewis [333] this early pain occurs in patients who have been walking or moving the affected limb at the onset of the occlusion The pain may be produced by manipulation of the extremity and evidently results from ischemia of muscle Ross[336] observed several patients with persistent severe pain localized to behind the

probable explanation of the initial sudden pain was irritation, caused by the impact of the embolus and the sudden distension of the artery of sensory nerves and sensory nerve endings in the adventitia of the occluded artery From observations on patients with arterial embolism, Seifert[illegible] in 1931 concluded that the initial sharp pain was due to arterial spasm and this view found fairly general acceptance. It is evident from the investigations of Lewis and associates on the effects of arresting the circulation in an extremity that muscle ischemia and not arterial spasm is the cause of the initial severe pain developing distal to an embolic occlusion According to Lewis,[2-3] muscle ischemia resulting from an inadequate collateral circulation in the region of the occlusion is also the cause of the initial severe pain that may be present at the level of an occlusion He has ascribed the pain in the loin in certain cases of embolic occlusion of the aorta to ischemia from involvement of the lumbar arteries by separate clots or by the main clot before its final lodgment at the bifurcation of the aorta Rykert and Graham[4] believe there are two types of pain in acute embolic occlusion one a sudden sharp pain of short duration often lasting a few minutes felt at the level of the occlusion and the other a more persistent diffuse aching pain felt distal to the occlusion in foot, calf or thigh if the patient has been using the affected limb at the onset of the occlusion. The sudden sharp pain at the level of the occlusion is referred to the loin or the front of the abdomen in occlusions of the bifurcation of the aorta or iliac artery respectively, and to the groin in upper femoral occlusion and always precedes the onset of numbness and coldness in the distal part of the affected extremity In a case of bilateral femoral emboli Richards[9] reports that he felt certain the onset of a sudden sharp pain in the groin marked the moment of lodgment of emboli in the femoral arteries Pain in the legs did not develop until the calf muscles were exercised He agrees that there are two distinct pains in some cases of embolism With the shifting of an embolic clot from the aortic bifurcation to the femoral artery the patient may complain of sharp pain in the back later in the lower abdomen and finally in the groin over the femoral artery It was our opinion that the short duration of the initial sharp pain at the level of an occlusion and the change in the location of the pain with a change in the position of the embolic clot occurring in certain cases made arterial spasm a more probable cause of this pain than muscle ischemia[4] The location of pain in patients with a segmental thrombotic occlusion of the lower aorta of insidious onset supports the conception that muscle ischemia resulting from an

release of vasoconstrictor tone in the treatment of an emolic occlusion is obvious

Diagnosis The early diagnosis of an acute embolic occlusion of a large artery should not present a difficult problem The important early findings are the sudden development of numbness and coldness usually with pain and absent pulsations in the distal arteries of the affected extremity A sudden sharp pain of short duration at the level of the occlusion or a diffuse aching pain in foot calf or thigh distal to the occlusion is present as an early symptom in 65 per cent of acute embolic occlusions The sudden onset of numbness and coldness of an extremity with or without pain in a patient with auricular fibrillation or a recent cardiac infarction makes the diagnosis of acute embolic occlusion almost certain Other clinical manifestations are pallor collapsed superficial veins impairment or loss of sensation diminished or absent tendon reflexes and weakness or loss of muscular power in the distal part of the extremity The site of the occlusion is usually the first bifurcation of a main artery above the level of coldness of the extremity With the aid of an oscillometer one can determine the presence or absence of pulsation in the deeper arteries at different levels in the affected limb

The differential diagnosis of embolism and thrombosis as a cause of acute arterial occlusion is a more difficult problem and a definite diagnosis may be impossible Important considerations are the age of the patient the nature of the associated primary disorder affecting the cardiovascular system the mode of onset of the occlusion, and the sequence in the development of peripheral signs and symptoms Occlusion from embolism may occur from youth to old age but acute thrombosis apart from that due to local trauma or arteritis from infection, rarely occurs before fifty Embolic occlusions occurring before fifty years of age usually are associated with rheumatic heart disease with mitral stenosis or subacute bacterial endocarditis, after fifty, with cardiac infarction from coronary thrombosis or with chronic myocardial disease from coronary sclerosis with auricular fibrillation As atherosclerosis of the aorta and its main branches is the common primary inciting factor in thrombotic occlusion it usually develops in older individuals with chronic myocardial disease with congestive failure The sudden onset of pain at the level of an occlusion is present in complete embolic occlusion but absent in a partial occlusion from emboli and in thrombotic occlusions Too often the clinician fails to distinguish between the sudden temporary, severe pain at the level of an occlusion and the continuous ischemic pain in the distal part of the extremity

knee or the calf and discovered a recent clot in the popliteal or posterior tibial artery Excision of a thrombosed popliteal artery was followed by complete relief of the pain, suggesting that the persistent pain localized in the popliteal space was due to a local arteritis

At the site of impaction of an embolus in a large artery the vessel is normal in diameter or slightly distended and the main artery and its branches distal to the occlusion are definitely constricted This reduction in caliber of arteries distal to the occlusion has been attributed to vasospasm due to a nervous reflex Kinmonth and Simone[98] have shown that the diameter of the upper third of the femoral and main arteries of the trunk which have a sensory but no sympathetic vasoconstrictor innervation coincides with the blood pressure in these vessels They suggest that shrinkage or decrease in caliber of these arteries distal to an occlusion is due to the fall in blood pressure and not to spasm

In arteries of the limb distal to the upper third of the femoral and in arteries forming the collateral circulation in acute occlusions of a large artery vasoconstrictor fibers play an important part in the control of the caliber of these vessels Mulvihill and Harvey [1] have shown that the cooling of the extremity of a dog which persists for several hours after ligation of the external iliac artery, could be relieved promptly by sympathectomy In man, Shepherd found that the release of vasomotor tone by indirect heating in experimental occlusion of the femoral artery in young healthy adults increased the blood flow in the calf 2 4 times over the resting flow without indirect heating He showed that this increase in blood flow was not due to a rise in general blood pressure but to a release of vasomotor tone in vessels forming the collateral circulation In embolic occlusion of the femoral artery, Gage and Ochsner [11] have observed the disappearance of numbness and the return of normal color and surface skin temperature in the affected limb following chemical block of the lumbar sympathetic ganglia It seems evident that the reduction in caliber and blood flow of the arteries of the extremity distal to an occlusion are due to two factors the fall in blood pressure and an increase in vasomotor tone Both these factors affect the 'critical closing pressure of small arteries In their study of the physical equilibrium of the wall of blood vessels Burton and associates[137] have shown that small arteries have a critical closing pressure which increases with increasing vasomotor tone and may close the vessel completely if the blood pressure falls below a certain value The importance of an early

upper extremity than in the lower, the collateral circulation in an acute occlusion is almost always adequate to meet the needs of the tissues distal to the occlusion In the lower extremity of older patients intimal thickening of the arteries of the collateral circulation may prevent adequate dilatation by appropriate measures, and atherosclerosis, with or without thrombosis of the main arteries of the leg impedes an adequate flow of blood to the calf and foot with the result that major nutritional changes including gangrene, develop

In a series of 100 cases of embolic occlusion treated at the Toronto General Hospital from 1938 to 1948[3, 4] gangrene did not develop in patients under thirty years of age but occurred in 27 per cent of patients from thirty to fifty, and in 44 per cent from fifty to ninety years of age The incidence of gangrene was higher in occlusions of arteries proximal to Poupart s ligament than in the occlusion of the popliteal but it is apparent that the higher incidence of gangrene in older patients is related to the known high incidence of arteriosclerosis In patients surviving an embolic occlusion the chief cause of an incomplete recovery of function in the affected extremity is pre existing arteriosclerosis of the arteries of the leg and foot

In patients successfully treated for an embolic occlusion, the late prognosis is poor and is dependent upon the pre existing heart disease and the recurrence of emboli in the peripheral arteries and, not uncommonly in the cerebral and mesenteric arteries In 1933, Pearse[339] reported that 52 per cent of patients subjected to embolectomy died within one month of operation The cause of death was cardiac failure or recurrent emboli operation being a negligible factor Strombeck,[340] who reported in 1935 upon the results of embolectomy in Swedish cases found that 60 per cent of patients died in hospital and that only 20 per cent were discharged from hospital with a restoration of the circulation 50 per cent of this latter group were dead in less than three years and two thirds in three years Fifty per cent of our patients with embolism of the femoral artery died within six months of the onset of the first occlusion In a series of 200 cases treated at the Massachusetts General Hospital from 1937 to 1953 Warren and associates[336(b)] report a hospital mortality of 37 per cent Jepson[377] reports a hospital mortality of 39 per cent It seems evident that earlier diagnosis and treatment have improved the immediate results in embolic occlusion but the late results remain unchanged

Treatment The main object in treatment is the early re establishment of an adequate peripheral circulation in the extremity distal to

which is present in both embolic and thrombotic occlusions Occasionally there may be a temporary absence of pulsation in the femoral artery at the onset of an acute femoro iliac vein thrombosis (phlegmasia alba dolens) or of an acute deep vein thrombosis causing no significant edema or cyanosis of the leg but resulting in pulmonary embolism In acute deep vein thrombosis absent arterial pulsations may be accompanied by coldness and numbness of the leg In contrast with acute embolic arterial occlusions, arterial pulsations absent at the onset of venous thrombosis return in a few minutes either spontaneously or after warming the body The temporary absence of arterial pulsation at the onset of acute venous thrombosis has been attributed to stimulation of sympathetic vasoconstrictor fibres

Prognosis If an early diagnosis is made and appropriate treatment promptly instituted, the immediate prognosis in the majority of cases of acute arterial occlusion is good as regards saving the affected extremity, but the late prognosis as far as length of life is concerned is poor If an adequate systemic blood pressure is maintained and the body kept warm, spontaneous recovery of the circulation after an embolus is the rule in the upper extremity and occurs in at least 25 per cent of occlusions of the femoral and popliteal arteries, and may occur in embolic occlusion of the aorta [330] With prompt and appropriate treatment, saving of the affected lower limb may be expected in 75 per cent of embolic occlusions [3 6(b)] If treatment is delayed for some hours, the slowing of the circulation from the low blood pressure in the main artery distal to the occlusion favors the development of secondary thrombosis in the main artery and its branches This distal thrombosis may block important collaterals entering the main artery distal to the occlusion and thereby prevent the development of an effective collateral circulation Thrombosis proximal to an embolus is less extensive and, according to Linton [438] rarely occludes the first major arterial branch of the collateral circulation proximal to the occlusion unless the general circulation is failing

Apart from early diagnosis and appropriate treatment, the recovery of an adequate circulation distal to an occlusion also depends on the presence or absence of significant sclerotic changes in the arteries of the collateral circulation and the main arteries of the leg and, to a lesser extent, upon the efficiency of the general circulation As there is a more abundant collateral circulation in the upper than in the lower extremity and sclerotic changes are less advanced in the arteries of the

pain, improve the color of the limb, and increase the skin temperature during treatment. If these effects are maintained for a longer period after each treatment one may expect the development of an adequate collateral circulation. The results of treatment of femoral occlusions by warmth to the body and the pavex boot equal those from embolectomy.[4] As the pavex boot requires careful adjustment to the limb by one experienced in its use, and treatments are prolonged, this method of treatment is being used less and less. Intermittent venous occlusion and the Sanders oscillating bed are simpler mechanical means of treatment to apply than pavex and continuous treatment is more comfortable for the patient. Linton[34] recommends intermittent venous occlusion and Allen *et al.*[1,2] the Sanders bed as adjuncts to other methods of treatment of embolic occlusion. These two methods of treatment should not replace reflex vasodilation by heat or procaine block of the sympathetic vasoconstrictor fibers as measures for producing maximal vasodilation of arteries of the collateral circulation. There is no evidence that these mechanical methods of treatment increase the blood flow through arteries forming the collateral circulation in occlusions above Poupart's ligament. Lewis and Grant[5] showed that the vasodilation reaction from venous compression in a limb is a local one and independent both of the central nervous system and local reflex, and Horton[343] has reported that one cannot get rid of the increased vasoconstrictor tone in the arteries of a limb, particularly in the feet, by the Sanders oscillating bed unless the environmental temperature of the patient is 28° C. (82° F.) or above that level.

The next important objective in treatment is the prevention of secondary thrombosis in the main artery and its branches distal to the occlusion by the administration of an anticoagulant. After Murray and Best[344] had shown that the anticoagulant heparin would prevent the development of thrombosis at the operation site following the removal of an embolism, anticoagulants came into fairly general use in both the conservative and operative treatment of embolic occlusions affecting the lower extremity. In arterial occlusions of the upper extremity anticoagulant therapy is not indicated, for spontaneous recovery of the peripheral circulation is the rule rather than the exception. Richards[330] and Allen *et al.*[1,2] advocate the administration of heparin as soon as a diagnosis of embolism is made, but it should not be administered in the home unless the attending physician is experienced in the use of anticoagulants. Richards recommends the intravenous injection of 100 milligrams of heparin every four to six hours until embolectomy is to

the occlusion As the impairment of the peripheral circulation is due not only to the occlusion of a main artery by embolism but also to increased vasoconstrictor tone of arteries forming the collateral circulation and of arteries of the limb distal to the occlusion, early maximal dilatation of these vessels should be the first object in treatment To promote vasodilatation the body should be wrapped immediately in warm blankets and surrounded by hot water bottles (45° C or 113° F) and the patient be given a drink of whisky or brandy[312] and an injection of morphine to control pain if present The affected extremity should be wrapped in cotton wool and kept in a dependent position, a few inches below the level of the heart *Hot water bottles should never be applied to the ischemic extremity for the relief of pain or in an effort to warm the cooling limb* The environmental temperature of the affected extremity should not be higher than 33° C or 90° F Refrigeration is contraindicated in the treatment of acute arterial occlusion

After preliminary treatment at home the patient should be transferred to hospital for further investigation and treatment In hospital reflex vasodilatation of arteries forming the collateral circulation and of the arteries of the extremity distal to the occlusion should be maintained In addition to warming the body by blankets and hot water bottles or a heat cradle, an unaffected upper extremity should be immersed in water at 43° C (109° F) or placed in an electrically heated box or sleeve Treatment by reflex vasodilatation may be supplemented but should not be replaced by the injection of vasodilator drugs the intravenous injection of one half to one grain (0 03-0 06 gm) of papaverine hydrochloride or 25 to 50 milligrams of priscoline Unless there is a prompt improvement in the collateral circulation following one injection, further treatment by vasodilator drugs is unlikely to be of value If an adequate collateral circulation does not develop in the limb in two hours following reflex vasodilatation by heat, with or without vasodilator drugs the appropriate sympathetic ganglia should be injected with procaine to produce a further release of vasoconstrictor tone of arteries forming the collateral circulation and the main arteries of the limb

Other methods recommended for the improvement of the circulation in the limb distal to an occlusion apart from embolectomy, are the alternate suction and pressure treatment (pavex) of Herrman and Reid intermittent venous occlusion of Collens and Wilensky,[298] and the Sanders [1] oscillating bed In patients seen before irreversible changes develop in the tissues of the limb, pavex treatment will relieve ischemic

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be performed or the fate of the ischemic limb is decided Allen *et al* recommended the administration of 50 milligrams of heparin intravenously every four hours at the beginning of treatment, the heparin to be replaced later by dicumarol if laboratory facilities are available They caution against the early administration of heparin if a paravertebral sympathetic block is planned as serious retroperitoneal bleeding may occur Since heparin is transported to the main artery distal to an occlusion by the collateral circulation, its effectiveness in the prevention of a distal thrombosis will depend on the establishment of an adequate collateral circulation which may require, in addition to reflex vasodilatation, a paravertebral sympathetic block Pratt[315] considers that technical errors in doing a block rather than the anticoagulant are responsible for the rare occurrence of serious bleeding

If the peripheral circulation of the limb does not show a satisfactory degree of improvement in two to five hours embolectomy should be considered A spontaneous recovery of the circulation may occur in embolic occlusions of the aorta and iliac arteries, but is uncommon Restoration of an adequate circulation following medical treatment occurs less often than after an early embolectomy In occlusion of the aorta and iliac arteries embolectomy is the treatment of choice if a diagnosis is made before irreversible changes develop in the tissues of the limbs and if the patient s general condition is not a contraindication to the operation It is well known that the immediate favorable results of embolectomy diminish rapidly if the operation is delayed more than ten hours after the occlusion,[339 316] but Murray[317] reports a successful result twenty-one hours after an occlusion of the aorta and both common iliacs using heparin during and following the operation to prevent the development of thrombosis at the site of operation When a patient is receiving heparin before operation its effect can be neutralized promptly by the intravenous injection of 50 milligrams of protamine sulphate if it is considered desirable In occlusions of the femoral and popliteal arteries, spontaneous recovery of the circulation occurs in 20 per cent of cases Medical rather than surgical treatment is generally recommended in occlusions of the popliteal artery In femoral occlusions the results of medical treatment compare favorably with those following embolectomy[3 8 330] When due consideration is given to the primary disease and the frequency of recurrent emboli, medical treatment would appear to be the treatment of choice in femoral occlusions Freeman *et al*[318] recommend arteriectomy for the relief of the intractable pain of ischemic neuritis which may occur as a late development

after acute embolic and thrombotic occlusions of the popliteal and femoral arteries

Thrombotic Occlusion The chief cause of acute thrombotic occlusion in larger arteries of older individuals is roughening of the intima from atherosclerosis with slowing of the circulation from myocardial disease with insufficiency In young individuals the most common cause would appear to be external trauma of the artery from a fracture dis location automobile accident, blow, or gunshot wound Other less frequent causes of acute thrombotic occlusion are a localized arteritis from infection, recurrent pressure from a cervical rib or crutch[89] and the thrombosing condition 'essential thrombophilia' Boyd and Wilde[349] have suggested that the fixation of the popliteal artery to the oblique ligament of the knee joint and a stretch strain on the artery may cause thrombosis of the popliteal Repeated crossing of the knees may be a predisposing cause In the past two decades an increasing number of cases of thrombotic occlusion of the lower abdominal aorta and iliac arteries of insidious onset have been reported The thrombus usually occludes the lower aorta, its bifurcation the proximal part of the common iliac and, less often a segment of the aorta or one iliac artery As the insidious onset of this type of thrombotic occlusion favors the de velopment of an effective collateral circulation, secondary thrombosis distal to the occlusion is limited and seldom if ever affects the restora tion of the circulation in the limb Atherosclerosis would appear to be the underlying cause of segmental arterial occlusion of major arteries Wylie and McGuinness[350] have reported cases of arteriosclerotic stenosis of aorta or iliac without thrombosis with symptoms of arterial insuf ficiency in the limb and suggest that atherosclerotic stenosis is an intermediary stage in the development of the arterial thrombosis

The signs and symptoms of an acute or sudden thrombotic occlusion are similar to those of an embolic occlusion with the exception that the sudden sharp pain of short duration that may be present at the level of an embolic occlusion does not occur The differential diagnosis of embolism and thrombosis in acute arterial occlusion is often a difficult problem In essential thrombophilia large and small arteries as well as veins are affected The blood should be examined for an excess of platelets and the bone marrow for hyperplasia of megalokaryocytes

Thrombotic occlusions of insidious onset of the large arteries above Poupart s ligament have a different symptomatology and run a different clinical course Leriche[351] was among the first to describe in detail the clinical manifestations of this type of thrombotic obliteration and it is

often called the Leriche aortic bifurcation syndrome The condition occurs in males from thirty to sixty-five years of age and runs a slowly progressive course for years According to Leriche, the early symptoms in occlusion of the aortic bifurcation are inability to keep a stable erection extreme liability to fatigue in both lower limbs, and pain on exercise in thighs and buttocks The chief physical findings are pulsation in the aorta above the umbilicus with absent pulsations in the groin and leg, global atrophy of both lower limbs, but no nutritional changes in the skin or nails Leriche stated that the arterial insufficiency of the limbs may be well borne for five or even ten years but always ends in gangrene, and sexual impotency becomes permanent These clinical findings have been confirmed by others There is general agreement that the earliest presenting symptom in a segmental thrombotic occlusion of one or more large arteries proximal to Poupart's ligament is pain on exercising in thigh hip, and calf Kekwick *et al*[3] found that the duration of intermittent claudication when patients were first seen varied from seven months to three years They examined fifty three consecutive cases of intermittent claudication in one or both lower extremities and found that there was arterial obstruction proximal to Poupart's ligament in 15 per cent Wasting of thigh and buttock was present In aortic occlusion, loss of sustained erection is reported by Elkin and Cooper[3 3] in 50 per cent of cases, and by DeBakey *et al*[3 1] in 33 per cent DeBakey considers the absence of nutritional changes in the skin and nails of the feet until late in the course of the disorder a significant feature As pointed out by Leriche, nutritional changes in the skin in aortic obstruction are not always bilateral and are preceded by a decrease in exercise tolerance of the calf muscles The late development of nutritional changes is likely due to sclerosis of the arteries of the leg and foot and not to the proximal thrombotic obstruction

Diagnosis A history of pain on exercise in the thigh or thigh and calf, usually of years' duration, pulsation of aorta above the umbilicus but absent pulsations in groin and leg and the absence or late development of nutritional changes in the skin and nails of the foot should suggest the diagnosis of a thrombotic arterial obstruction of insidious onset above Poupart's ligament In aortic bifurcation obstruction, loss of sustained erection may be the presenting symptom The diagnosis may be confirmed by aortography

Prognosis In acute thrombotic occlusion the prognosis depends on the cause of the thrombosis—arteriosclerosis trauma, or infection—and on the age of the patient If a younger patient recovers from the direct

effect of trauma and if gangrene does not supervene rapidly a steady improvement in the circulation usually results In older patients gangrene may result or the restoration of the circulation is slow and recovery incomplete because of pre existing sclerosis of coronary aorta and peripheral arteries Patients with thrombotic occlusion of insidious onset of arteries proximal to Poupart s ligament carry on for periods up to twelve years after the onset of intermittent claudication without development of gangrene of the feet Apart from an aortic thrombosis causing sexual impotence or occluding one renal artery a rare complication the primary arterial thrombosis plays a minor role in determining the end result of the disorder The important determining factor would appear to be arteriosclerosis affecting either the arteries of the leg and foot and terminating in gangrene or the coronary or cerebral arteries causing death from coronary or cerebral thrombosis

Treatment The initial treatment of acute thrombotic occlusion apart from the treatment of trauma or infection is the same as that outlined for the medical treatment of embolic occlusion If an effective collateral circulation is not established after prolonged medical treatment and lumbar sympathectomy, and major nutritional changes in the skin of the foot are absent local surgical treatment of the thrombosed artery should be considered Leriche[3] recommended arteriectomy and dos Santos[356] disobliteration and arteriectomy in the treatment of the non acute stage of thrombotic occlusions These operations have not come into general use Ross[336] has reported complete relief of severe pain behind the knee or in the calf as well as in the foot following the excision of a thrombosed popliteal artery and Boyd and Jepson[357] a marked increase in exercise tolerance of the thigh and leg in a young man following the excision of a thrombosed external iliac artery which had resulted from trauma Reboul and Laubry[358] have reported favorable results in selected cases from the dos Santos operation More recently resection of the thrombosed artery and replacement by a graft artery or vein has been advocated but it is too early to assess the late results of this operation

In thrombotic occlusion of insidious onset methods of treatment will depend on the age of the patient, the duration and rate of progression of presenting symptoms and the presence or absence of major nutritional changes in the skin and nails of the feet In patients over sixty years of age and in all patients with major nutritional changes with or without gangrene treatment as outlined for obliterative vascular disease from arteriosclerosis is indicated In younger male patients with

a segmental aortic bifurcation thrombosis and loss of sustained erection and absence of major nutritional changes in the feet, the ideal treatment is resection of the thrombosed artery and a graft replacement, as recommended by DeBakey *et al.*[354] Leriche[351] has reported that the loss of sustained erection may disappear after a bilateral lumbar ganglionectomy but that sexual impotence becomes permanent without surgical treatment. If pain in the calves on exercise has increased in recent months or minor nutritional changes are present in the skin of the feet, a resection and replacement operation should not be undertaken without the examination by arteriography of the arteries of the legs and feet. If significant signs of intimal sclerosis, with or without thrombosis of the main arteries of the leg and foot, are present, the major operation of resection and replacement would be of limited value. Preliminary medical treatment followed by a lumbar ganglionectomy should be considered. A ganglionectomy will not result in any significant improvement in the exercise tolerance of the calves but should slow the development of nutritional changes in the skin and promote the healing of any minor open lesions present. In unilateral segmental thrombosis of the common iliac or external iliac, the collateral circulation is usually adequate to meet the ordinary nutritional needs of the tissues of the affected extremity. Unless intermittent claudication limits the walking distance demanded by the occupation of the patient, the major operation of resection and replacement would not appear to be indicated.

Arteriovenous Fistula

The term 'arteriovenous fistula' is applied to conditions in which there is an abnormal communication between artery and vein by which the arterial blood enters the vein without passing through the capillary system. There are two types of arteriovenous fistula: the acquired and the congenital. The former results from trauma, the origin of the latter is a developmental anomaly. In the acquired type the fistula is usually single and caused by a penetrating wound of a large or medium sized artery and the accompaning vein from a knife stab or a bit of glass or steel. The vessels most commonly injured are the femoral, popliteal, subclavian, axillary, and brachial. The communication between artery and vein may be direct but more often a sac intervenes and the term 'arteriovenous aneurysm' is commonly applied to the acquired type of arteriovenous fistula. In the congenital type, multiple communications

between artery and vein are present as a result of the persistence of anomalous communications between arteries and veins which develop in the capillary plexus of the embryo [3, 9, 360, 361] Medium sized vessels of the head (extracranial and intracranial) the neck, and the extremities are affected Prior to the development of the present understanding of the origin of the fistula and the signs and symptoms in congenital arteriovenous fistula terms descriptive of the late local manifestations of this condition were applied such as arteriovenous varix arteriovenous aneurysm cirsoid aneurysm racemose aneurysm aneurysm by anastomosis and pulsating angina

William Hunter in 1757 was the first to recognize an abnormal communication between artery and vein and to describe the clinical manifestations of the acquired type of arteriovenous fistula According to Dean Lewis[36] Letenneur in 1859 was the first to report a case of congenital origin but Callander[363] credits Busche in 18 7 The circulatory disturbances in both the acquired and congenital types of arteriovenous fistula are essentially the same Clinical and experimental studies have shown that these depend upon the location and size of the abnormal communication or communications between artery and vein and upon the rate of development and duration of the leak Among important contributions to the subject of arteriovenous fistula are those of Makins [11] Matas [364] Halsted [36] Callander [363] Leriche [366] Reinhoff [361] Reid [367] Holman [368] Lewis and Drury [369] Dean Lewis [36] Pemberton and Saint [370] and Horton [371]

Acquired Arteriovenous Fistula In a non fatal penetrating wound of a large superficial artery and vein a sac often forms at the site of the hematoma between artery and vein and provides a permanent communication between these vessels Following recovery from immediate effects of the wound and the healing of the point of penetration the patient may notice a purr and a swelling in the region of the wound or a dilation of the superficial veins with swelling of the limb He may complain of an aching and heaviness of the extremity on exertion with or without palpitation or shortness of breath On physical examination a continuous thrill and murmur most marked at each systole of the heart and an expansile swelling in the region of the damaged vessels are found The skin on the area is warmer than on the corresponding area in the normal extremity The affected artery proximal to the fistula is dilated and the pulsation more forcible than in the normal extremity Later the affected vein and its tributaries are dilated and often tortuous from increased venous pressure and a pulsation synchronous with the

arterial pulse may be present The affected extremity distal to the fistula is larger than the normal one, due to the dilated veins If much of the arterial blood to the extremity is diverted through the fistula into the venous system without passing through the capillaries then general circulatory manifestations are similar to those found in aortic insufficiency[368] with the exception that no diastolic murmur and a lower systolic pressure are found an increase in pulse rate, water-hammer pulse capillary pulsation a low diastolic pressure, a raised pulse pressure, and a difference in the arm leg systolic pressure (Hill s sign) After the establishment of an arteriovenous fistula the systolic pressure at first is lower than normal but it gradually returns to a normal level During the stage of adjustment of the circulation the heart is enlarged first from dilation and later from dilation and hypertrophy The general venous pressure is normal[369-370] unless signs of cardiac failure develop As an indication of the effect of the fistula on the general circulation, closure of the artery proximal to the fistula, by digital pressure, results in slowing of the pulse (Branham s sign) and a rise in diastolic pressure If the cardiovascular system is unable to compensate for the added burden of a reflux of blood the decreased flow of blood through the capillaries of the affected extremities leads to the development of varices edema and pigmentation with or without ulceration, and signs of cardiac failure may develop if the fistula is not permanently closed by operation On the other hand in certain patients an effective collateral circulation is established distal to the fistula the temperature of the skin of the toes is higher than normal indicating an increased blood flow If the fistula is acquired during the period of growth before the epiphyses close, there is an increase in the length of the extremity

Studies on the physiological effects of an arteriovenous fistula have resulted in a much clearer understanding of the origin of signs and symptoms and of the adjustment in the circulation that may take place Following the establishment of an arteriovenous fistula arterial blood enters the damaged vein under arterial pressure, causing a marked increase in the pressure of the vein and its tributaries, the veins dilate and later their walls become hypertrophied The oxygen saturation of the blood in veins near the fistula approaches the saturation of arterial blood The increase in girth of the limb in the early stages at least, is due to an overfilling of the veins The general venous pressure is normal unless cardiac failure is present The low diastolic pressure is due to the reflux of blood into the veins The dilation of the veins in the affected ex-

tremity of the artery proximal to the fistula and of the chambers of the heart is accompanied by an increase in blood volume The heart rate is accelerated and the cardiac output increased to maintain an effective general circulation If the fistula is large the increased work of the heart from the reflux of blood into the veins without passing through the capillaries causes first a dilation and later hypertrophy of the heart muscle If the fistula is permanently closed by operation the heart decreases in size, the heart rate is slowed, the cardiac output and the blood volume approach the normal, and a rise occurs in the general systolic and diastolic blood pressures

Congenital Arteriovenous Fistula A congenital arteriovenous fistula is much less common than the acquired type and occurs with equal frequency in males and females Multiple anomalous communications exist between the arteries and veins In one type there are small lateral communications between the artery and the accompanying vein without involving the continuity of the main vessels in the other type the communication is more direct with an end to end anastomosis between arteries and veins Reinhoff[311] observed a greater and more rapid dilatation of vessels near the fistula in the latter type A congenital arteriovenous fistula may manifest itself at or shortly after birth or the anomalous communications between artery and vein may remain latent in the early years of life At or shortly after birth, the mother may notice a *small swelling over which the skin is warmer and the affected part* larger than the corresponding part on the normal side Often the swelling develops in a birthmark—a capillary nevus Later, the child may complain of a throbbing or a purring noise in the affected part The first manifestation may be a swelling with dilation and tortuousity of superficial veins with or without ulceration A strain or a contusion may mark the onset of the local circulatory manifestations or be followed by an increase in the severity of pre existing signs and symptoms On physical examination the findings in general are similar to those in the acquired type but thrills and bruits are absent over multiple small anomalous communications particularly deep seated ones

Diagnosis The diagnosis of an acquired arteriovenous fistula is usually simple A history of a penetrating wound and the subsequent development of a local swelling with a continuous thrill and murmur throughout the cardiac cycle an increased surface temperature and a dilatation of veins establish the diagnosis In the congenital type diagnosis may be difficult especially in the absence of a birthmark no local swelling may

be present and a thrill and murmur are often absent Varicose veins with or without ulceration, in one extremity, increase in surface temperature, and an increase in the girth and length of part of an extremity occurring in a young person should make one suspect a congenital arteriovenous fistula even in the absence of a birthmark, local swelling thrill or murmur, a high oxygen saturation of blood from a vein in the area confirms the diagnosis Arteriography by the injection of a radiopaque substance, such as thorotrast, into the artery proximal to the suspected site of the fistula will confirm the diagnosis and indicate the exact location, number, and size of the anomalous communications

Prognosis In untreated cases of arteriovenous fistula, the prognosis depends upon the rate of development and the duration of the local and general circulatory disturbances In the acquired type, a small leak may heal spontaneously a few months after the injury When troublesome local disturbances or signs of cardiac insufficiency develop the condition tends to run a progressive course Cardiac failure is a common cause of death in the acquired type

Treatment The treatment of the acquired type of arteriovenous fistula is surgical In the hands of experienced surgeons, the results of operative treatment are good The operation should be performed within three to six months after the injury[367] to prevent the development of cardiac and other disturbances This allows time for the possible spontaneous healing of the leak or the development of an adequate collateral circulation before operation In congenital arteriovenous fistula, the presence of multiple communications makes successful treatment by operation difficult or impossible Few such cases have been treated successfully Ulceration in the lower extremities from chronic venous insufficiency has been treated effectively by para rubber bandages[371] Amputation may be a necessity

Periarteritis Nodosa—Polyarteritis

Periarteritis nodosa is an inflammatory panarteritis affecting segments of any of the medium-sized and small muscular arteries, the arterioles, and the capillaries, accompanied by systemic manifestations of a subacute infection and local disturbances depending upon the site or sites of the arterial lesions According to Dickson[373] the first case was observed by Rokitansky in 1852, but Kussmaul and Maier,[374] in 1866 were the first to describe the clinical and pathological findings and to give the condition the name 'periarteritis nodosa' Since then over 400

cases have been reported in the literature but over half of these have been reported in the past decade As all cases are not reported the clinical diagnosis is difficult and chronic lesions are easily missed at routine autopsy the disease is more common than is generally recognized

Etiology Periarteritis nodosa may occur at all ages—two and one-half months to seventy eight years—but is more commonly found in the third and fourth decades It affects males much more often than females The cause of the disease has remained obscure At one time syphilis was considered a cause but it is now definitely excluded A filterable virus was suggested[375] as the etiological agent but this has not received confirmation Harbitz[376] expressed the view that the inflammation of the artery was of an infectious toxic nature Klotz[3] and Ophuls[378] called attention to the similarity between certain clinical and pathological findings in periarteritis nodosa and rheumatic fever and suggested infection as the inciting factor From an exhaustive study of periarteritis nodosa Gruber[3 9] maintained that the vascular reaction is a hyperergic phenomenon resulting from different infections The work of Swift and his associates[380] on rheumatic fever lent support to the conception that hyperergy is of importance in the pathogenesis of periarteritis nodosa Klinge[381] has shown that rheumatic fever primarily affects the fibrous connective tissues and has expressed the view that rheumatic lesions are manifestations of a hyperergic tissue reaction Klinge and Vaubel[3 ( )(b)( )] are in agreement with Klotz and Ophuls as to the similarity of the lesions in rheumatic fever and periarteritis nodosa They have produced lesions in animals by the administration of foreign protein which closely simulate those of rheumatic fever and periarteritis nodosa More recently, Rich observed vascular lesions characteristic of periarteritis nodosa in patients who had hypersensitive reactions following the therapeutic injection of an antiserum[383( )] and the administration of sulphonamides[383(b)] By the administration of sterile horse serum in experimental animals Rich and Gregory produced vascular lesions characteristic of periarteritis nodosa[384(a)] and cardiac lesions having the basic characteristics of those of rheumatic carditis[384(b)] They consider the lesions in periarteritis nodosa and rheumatic fever to be manifestations of hypersensitivity of the anaphylactic type It has been observed that the lesions of periarteritis nodosa can result from allergic reactions from other substances such as thiourea[385] iodine[386] sodium dilantin[387] and proteins of infecting microorganisms[379] It seems clear that the vascular lesions in periarteritis nodosa are usually if not always

manifestations of a hypersensitivity or allergic tissue reaction in the affected arteries which may be caused by different sensitizing antigens

Pathology According to Gruber[379] and Arkin,[388] arterial lesions affect various parts of the body in the following order of frequency kidney, 75-80 per cent heart, 65 70 per cent, liver, 65 per cent, gastro intestinal tract 45 50 per cent, mesentery, 30 per cent, muscles, 30 per cent, pancreas 25 30 per cent, genitalia, 20 per cent, peripheral nerves, 20 per cent, spleen and adrenals 15 per cent, brain, 8 per cent, and, less often lungs, pleura, ureters, and lymph nodes Vascular lesions characteristic of the acute, subacute, and chronic or healed stages of the disease are usually present The process may affect a part or the entire circumference of a segment of an artery Arkin has described four stages in the pathological process The earliest lesion consists in edema of the media with separation of muscle and elastic fibers by a fibrinous exudate and necrosis of the media Ischemia of the media, resulting from the early damage of nutrient vessels to the affected artery from the hypersensitive reaction, would appear to be the chief cause of necrosis In the second or acute inflammatory stage, the fibrinous exudate extends into the intima and adventitia, the media and adventitia are infiltrated by polymorphonuclear neutrophils and sometimes eosinophils, lymphocytes, and plasma cells, subendothelial proliferation develops in the intima and may result in secondary thrombosis and infarction of an organ supplied by the affected vessel Necrosis of the media may result in the formation of an aneurysm which may rupture and cause death from hemorrhage In the third or granulation tissue stage there is a marked proliferation of fibroblasts from the adventitia into the media a pronounced increase in mononuclear cells and eosinophils, and a decrease in polymorphonuclear neutrophils There is progressive proliferative thickening of the intima causing narrowing of the lumen and even obliteration of the artery Nodules are commonly found along the smaller arteries They may be produced by the inflammatory reaction but are more often the result of aneurysmal dilatation In the fourth or healed stage, the wall of the affected artery is replaced by scar tissue and its lumen may be obliterated

Fibrinoid necrosis of fibrous connective tissue would appear to be a basic characteristic of the pathological process in periarteritis nodosa and justifies the inclusion of this disease in the group of diffuse collagen diseases[389] The lesions are found in medium sized and small muscular arteries and arterioles and may spread from arteriole to capillary and venule The cause of their more frequent localization in the arteries

of certain organs is unknown Arterial lesions in the lungs are uncommon, lesions of the larger pulmonary arteries are rare but the bronchial arteries and the smaller pulmonary arteries and arterioles may be affected It is stated that veins are involved but there is no satisfactory evidence that medium-sized and small veins are primarily affected Veins in close proximity to arteries as in the portal system of the liver may be involved by an extension of the periarteritis[8] Ophuls[3,8] observed an infiltration of the adventitia of small veins with leucocytes chiefly eosinophils and in a few instances, swelling of the endothelium with proliferation

Symptoms The onset of illness in periarteritis nodosa may be acute but more often is insidious The disease may run an acute, subacute or chronic course and be characterized by remissions and exacerbations The systemic manifestations of malaise general weakness tachycardia sweating, loss of weight and a low grade fever suggest an infectious disease These may be present for weeks or months before the development of more acute general or local signs and symptoms With the development of moderately high fever and local manifestations a polymorphonuclear leucocytosis is constant and varies from 15 000 to 30 000 or more Eosinophilia occasionally excessive, is often present The erythrocyte sedimentation rate is increased with an associated rise in plasma fibrinogen[330] The arterial lesions produce local symptoms either from rupture of an aneurysm with hemorrhage or from nutritional disturbances in an area resulting from partial or complete arterial occlusion As arterial lesions causing symptoms may be confined to one area or disturbances of function may be more marked in one region Harbitz[3,4] classified cases of periarteritis nodosa into different types such as abdominal neuromuscular, cutaneous renal cardiac, and cerebral Usually a combination of two or more types is present

In the abdominal type common symptoms are abdominal distress or, more often severe pain anorexia nausea vomiting jaundice constipation or melena The symptoms vary with the vessels affected gastric mesenteric heaptic cystic, splenic, or pancreatic The clinical manifestations in the neuromuscular type suggest a polymyositis or polyneuritis The chief symptoms are aching pains cramps muscle tenderness pain along peripheral nerves paresthesia and muscle weakness with signs of peripheral neuritis Neuritic manifestations would appear to be due to ischemia of the nerves resulting from lesions of their nutrient arteries[391] and not to any direct toxic effect on the affected nerves In the kidney the vascular lesions may cause infarction of the kidney or a

focal or diffuse glomerulonephritis As the arteries of the kidney are the ones most commonly affected in periarteritis nodosa, abnormal urinary findings are a frequent occurrence These consist of albuminuria and cylindruria less often microscopic hematuria, and occasionally macroscopic hematuria Nitrogen retention may develop and renal insufficiency is a common cause of death A systolic or diastolic hypertension, or both is present in about 65 per cent of cases[392 393] The development of a diastolic hypertension during the course of the disease usually is associated with arteriolar necrosis or sclerosis of the kidney but changes in the fundus oculi characteristic of malignant hypertension may be absent Vascular changes in the intramuscular branches of the coronaries may result in dilatation and hypertrophy of the heart Congestive heart failure may develop and cause death Renal, cardiac, and less often, muscle lesions may be the cause of edema which is present in about 50 per cent of cases In the cutaneous type, erythematous urticarial, or purpuric lesions may be present Gangrene of the fingers and toes has been reported[394] A segment of a superficial artery may be tender and present nodular thickenings Cerebral manifestations may simulate meningitis or tumor of the brain Convulsions, signs of a retrobulbar neuritis, cerebral hemorrhage, or thrombosis may be present Pulmonary symptoms are uncommon, asthma is reported in 12 to 18 per cent of cases[395 396] A lesion of the bronchial artery may be a cause of hemoptysis Pain and moderate swelling of joints may be present A moderate enlargement of superficial lymph glands is not uncommon

Diagnosis The clinical diagnosis of periarteritis nodosa is a difficult problem A diagnosis of periarteritis nodosa usually has followed a biopsy of a tender superficial artery or tender muscle or of a lesion in the abdomen at an operation for appendicitis, cholecystitis, mesenteric thrombosis or hemorrhage, but clinical diagnosis is becoming more frequent Meyer[397] stressed the combination of chlorotic marasmus, polymyositis, polyneuritis and abdominal symptoms in the diagnosis of periarteritis nodosa In patients giving a history of systemic manifestations characteristic of a low grade infection, which become progressively worse, and developing moderately high fever or disturbances of function related to two or more parts of the body, such as abdominal and neuromuscular symptoms one should suspect periarteritis nodosa The combination of a polymorphonuclear leucocytosis of 15 000 or over with an eosinophilia and abnormal urinary findings justifies a tentative diagnosis of periarteritis nodosa In view of the allergic nature of the vascular lesions a careful history may reveal possible sensitizing

agents and lend support to the diagnosis An upper respiratory tract infection may precede the onset of the disease and result in an exacerbation of pre existing symptoms

Prognosis The prognosis is generally bad In the acute and subacute forms of the disease the mortality is over 90 per cent, the duration of the disease varies from a few weeks to a few months with an average of about six months A few patients recover from the acute attack and live from two to four years Spontaneous recovery may occur two of our patients, in whom the diagnosis of periarteritis nodosa was confirmed by biopsy, have had no relapse of the disease in over fifteen years There is abundant evidence that vascular lesions heal, but proliferative tissue changes tend to obliterate the lumen of the artery partially or completely, and the decreased blood flow impairs the function of the affected organ Baggenstoss *et al*[398] report complete healing of all arterial lesions in two fatal cases but the proliferative vascular changes resulted in infarction of kidney heart and intestinal tract In the chronic stage of the disease the usual cause of death is cardiac or renal insufficiency

Treatment Until Hench and associates[399] in 1949 announced the dramatic effects of adrenocorticotrophic hormone (ACTH) and of cortisone in the collagen disease rheumatoid arthritis the treatment of periarteritis nodosa was symptomatic Since 1949 a number of patients with periarteritis nodosa have been treated by ACTH or cortisone and reports published on the effects of hormone therapy in one or a small group of patients There is general agreement that hormone therapy is effective in controlling the clinical manifestations in the acute and subacute stages of the disease but is not a cure for the disease The symptoms of malaise, fever anorexia and aching pains are relieved promptly and the erythrocyte sedimentation rate falls to normal or nearly normal[390] Attacks of asthma are relieved but no significant improvement in peripheral neuritis is observed[398 400] After cessation of therapy, there is a complete remission of symptoms in some patients but its duration has yet to be determined some patients have a partial relapse which is again controlled by hormone therapy In still other patients the initial improvement is not maintained and their condition becomes progressively worse resulting in death

The prompt initial response to hormone therapy is attributed to its effect in suppressing the hypersensitivity tissue reaction in the arterial lesions Berthong *et al*[401] found that sixteen of nineteen animals sen

sitized with horse serum and given antigen, according to the method of Rich and Gregory, developed polyarteritis and cardiac lesions and that only five of nineteen animals sensitized and given antigen in like manner but treated with ACTH developed lesions In two patients dying shortly after hormone therapy was discontinued, Baggenstoss *et al* [394] found no histological signs of active inflammation in the arterial lesions within three weeks and three months, respectively, after a biopsy had shown signs of active inflammation in an arterial lesion From these observations it would appear that early hormone therapy might prevent the later proliferative vascular changes which impair the function of the organs affected and ultimately cause the death of the patient The importance of early diagnosis and adequate hormone therapy is evident

Cortisone and ACTH are equally effective in the treatment of periarteritis nodosa As cortisone is effective by mouth,[40, 403] the ease of oral administration has made it the hormone of choice in treatment The usual starting dose is 200 to 300 milligrams, in divided doses at intervals of six hours, for the first day, treatment is continued with a daily dose of 150 to 200 milligrams until symptoms are controlled, and then decreased to a minimal maintenance level for the control of symptoms The daily maintenance dose should be continued for a period of six weeks and then gradually decreased before discontinuing the treatment In some patients the continuation of a daily maintenance dose of 100 milligrams is required to suppress symptoms this dosage may be continued for two years or longer without ill effect [390] If a relapse occurs after a complete remission of symptoms, the course of treatment with cortisone should be repeated

Temporal Arteritis—Giant-cell Arteritis

Temporal arteritis was first described by Jonathan Hutchinson[404] in 1890 but no other cases were reported in the literature until Horton, Magath, and Brown,[40 (a)(b)] in 1932, described the clinical and pathological findings in two cases of temporal arteritis which seemed to represent a definite clinical syndrome Since then over seventy cases have been observed at the Mayo Clinic and a greater number have been reported in the literature on this continent and in England The symptoms and pathological findings are fairly uniform the disease may be considered a definite clinical entity

The etiology remains obscure Temporal arteritis develops in patients over fifty-five years of age, females are more commonly affected

than males The inflammatory reaction in the artery—periarteritis and arteritis—suggests infection as a probable cause but no microorganisms have been found Allergy is not a causal factor

The vascular lesion is one of a subacute or chronic periarteritis It is usually confined to a segment of one or both superficial temporal arteries but may be present in the transverse facial, occipital, and retinal arteries Lesions closely simulating those found in the temporal arteries have been observed in the aorta external and internal carotids iliac mesenteric renal and peripheral arteries Cooke and associates[406] regard this form of arteritis as a generalized vascular disease The inflammatory process would appear to begin in the adventitia as a subacute periarteritis and spread by the vasa vasorum to the media in which the earliest lesion is a focal necrosis Later the area of necrosis is infiltrated with lymphocytes plasma cells and large mononuclear cells followed by fibroblastic proliferation and often the appearance of foreign body giant cells Because of the presence of multinuclear giant cells in most of the affected arteries examined by Gilmour,[407] he called the disease giant cell chronic arteritis The intima is thickened but rarely infiltrated by cells from the media The lumen of the artery is narrowed from intimal thickening and secondary thrombosis which is rapidly organized is common In contrast with periarteritis nodosa the medial necrosis is focal and not diffuse polymorphonuclear neutrophils and eosinophils *are sparse or absent and aneurysmal dilatations are rare* The inflammatory reaction more closely resembles the lesion in thromboangiitis obliterans

The onset of the illness may be insidious or acute and is characterized by systemic manifestations of general malaise tiredness anorexia loss of weight, and aching pains in head joints and muscles After a few weeks or months a severe persistent headache develops usually in one or both temporal regions with tenderness over the temporal artery Occasionally the severe headache is in the neck or back of the head and tenderness of the occipital artery is present Tenderness of the scalp and pain over the tempero mandibular joint with difficulty in mastication are common In about half the cases severe headache is followed by ocular disturbances such as pain in the eye diplopia blurring of vision diminished or total loss of vision One or both eyes may be affected Loss or impairment of vision is usually preceded by ocular pain Barnett[408] considers ocular pain which is usually retrobulbar and fleeting visual disturbances ominous premonitory signs of a serious impairment of vision and an indication for immediate treatment with

cortisone or ACTH Mental confusion, delirium, and coma have been observed With the development of the acute local manifestations of the disease, the systemic symptoms increase in severity A low grade or moderate fever is present, the erythrocyte sedimentation rate is increased, the leucocytes are normal or show a moderate increase with no eosinophilia and a moderate anemia is present

In uncomplicated cases there are no abnormal urinary findings On examination of the affected temporal artery the overlying skin may be reddened the vessel is tender, thickened, often nodular, and tortuous At first a pulsation may be present but it later disappears with occlusion of the artery from intimal thickening with or without thrombosis Necrosis of the scalp may develop over the affected artery If ocular disturbances are present, one may find weakness of the oculomotor muscles and, in the fundus oculi, mild edema, small hemorrhages exudates, scotomata, or often atrophy Changes in the fundus oculi are due chiefly to an arteritis of the central retinal artery or a branch arteriole or to an ischemic optic neuritis resulting from arteritis[409]

Diagnosis Temporal arteritis should be suspected whenever a patient over sixty years of age complains of pain and tenderness over the temporal arteries and/or sudden dimness or loss of vision accompanied by systemic manifestations of a low grade fever and a high erythrocyte sedimentation rate

Prognosis Temporal arteritis is a chronic segmental vascular disease usually terminating after several months, in healing of the arterial lesions If the lesions have their usual localization in the superficial temporal arteries and their branches, with or without involvement of the central retinal artery or branch arterioles, the disease runs a relatively benign course Partial or complete obliteration of affected arteries may persist, but the chief disability is impairment or loss of vision If visual impairment has persisted for a week or more, it is permanent The common causes of death both in the active and healed stages of the disease are coronary and cerebral thrombosis From a critical analysis of reported cases Crosby and Wadsworth[410] concluded that the mortality from the disease was 12 5 per cent In a few patients dying of a cerebral thrombosis and examined post mortem a giant cell arteritis has been found in the internal carotid Cerebral thrombosis would appear to be a direct or indirect cause of death in certain cases of temporal arteritis A few cases have been reported with lesions in the terminal branches of the coronaries[406, 411] essentially similar to temporal arteritis but there was no satisfactory evidence that the lesions were a

cause of cardiac infarction or cardiac insufficiency Atherosclerosis of the main branches of the coronary is the most likely cause of cardiac deaths in cases of temporal arteritis and probably the most common cause of cerebral thrombosis

Treatment Until the introduction of cortisone and ACTH the treatment of temporal arteritis consisted of the administration of analgesics and often the excision of an involved segment of the temporal artery for the relief of headache Excision relieved the persistent headache but did not alter the course of the disease The initial effect of cortisone or ACTH on the local and systemic manifestations in temporal arteritis is similar to the favorable and often dramatic effect observed in periarteritis nodosa with the exception that the erythrocyte sedimentation rate remains high[408 41] As pointed out by Whitfield *et al*[41] the erythrocyte sedimentation rate may remain elevated for weeks or months after other manifestations of active disease have subsided When cortisone is administered in the dosage recommended for the treatment of periarteritis nodosa malaise fever nausea headache and tenderness of the scalp disappear in the first three days of hormone therapy From present experience it seems evident that adequate hormone therapy will control the local and systemic symptoms of active disease and will safeguard any vision that remains after the therapy has been started[143] If the hormone is stopped too soon or the daily dose decreased too rapidly during the initial course of treatment there is a prompt return of symptoms indicating that the tissue reaction in affected arteries is suppressed but not healed and that a maintenance dose of hormone is necessary until natural healing of the lesions occurs In view of the known wide variation in the duration of symptoms of active disease in different patients and the persistence of a raised erythrocyte sedimentation rate for weeks or months after the control of symptoms by hormone therapy, it is evident that the duration of hormone therapy and the maintenance dosage must vary from patient to patient After the maintenance dose has been determined it should be continued for two months or longer and then gradually decreased A daily dosage of 25 to 75 milligrams of oral cortisone should be continued for a further period of six months or until the erythrocyte sedimentation rate is normal

Whitfield *et al*[41] observed no improvement in vision following hormone therapy in patients with partial loss of vision of long standing or total blindness of more than a week Patients with partial loss of vision for ten days or less showed some improvement but in none was normal

sight restored The prevention of impairment of vision by early diagnosis of the disease and adequate hormone therapy is, therefore, important

Other Forms of Acute Arteritis

Acute inflammatory lesions of the arteries, including the arterioles and capillaries occur in many diseases other than those already discussed A suppurative inflammation, the direct effect of bacteria, may be caused by the extension of the inflammation from an abscess in adjacent tissues or by an infected embolus from vegetations in bacterial endocarditis An infected embolus may lead to the development of a mycotic aneurysm with rupture and hemorrhage In syphilis, the infection may involve the aorta or reach the small arteries of the meninges along the perivascular lymphatics and vasa vasorum, producing a non suppurative inflammation with proliferative intimal thickening—syphilitic endarteritis Inflammatory lesions caused by bacterial products may represent an allergic reaction, as in rheumatic fever In another group of diseases such as disseminated lupus erythematosus and Libman Sacks syndrome it would appear that bacteria or their products are not the cause of the vascular lesions, the etiological agent or agents are unknown

Karsner[413] has applied the term 'secondary arteritis' to those forms of acute arteritis in which bacteria are present and the term 'primary arteritis' to those in which infective agents have not been demonstrated Primary arteritis occurs in diseases which primarily affect fibrous connective tissues[381] and the term 'diffuse collagen disease'[389] has been applied to this group of diseases As pointed out by Duff,[414] 'All of the lesions display in varying degree, and in different combinations the three aspects of the pathological process the degenerative or destructive alteration as represented by fibrinoid necrosis, the proliferative changes which are ultimately productive of varying quantities of dense collagenous connective tissue, and thirdly the inflammatory reaction to the primary connective tissue injury In rheumatic fever and periarteritis nodosa it seems clear that the primary arteritis is an allergic tissue reaction, but allergy would not appear to play a role in the vascular lesions of disseminated lupus erythematosus'[415] For details of diseases primarily affecting connective tissues the reader is referred to sections elsewhere in Oxford Medicine which deal more specifically with these different disorders

Tumors of Blood Vessels

A localized dilatation, hyperplasia or new growth of vessels forming the capillary system—arteriole capillary and venule—is not uncommon Lesions having one or other of these vascular changes or a combination of them will be discussed under the following headings (1) telangiectasis—an acquired dilatation of pre existing vessels (2) vascular nevus—a congenital dilatation and hyperplasia of existing vessels, (3) hemangioma—a benign new growth of blood vessels, (4) hemangio endothelioma—a malignant new growth of blood vessels

Telangiectasis Telangiectasis is an acquired localized dilatation of small vessels chiefly capillaries and venules The lesions usually are multiple and occur most commonly on the cheeks nose, neck and chest but may occur on other parts of the body including the mucous membranes The chief characteristic of the lesion is a dilatation of pre existing capillaries and venules, thinning of the walls and tortuosity of the affected vessels may be present Telangiectases occur on the neck of persons exposed to wind and cold in areas treated by X ray and radium and in association with dermatological conditions such as lupus erythematosus acne rosacea xeroderma pigmentosum, and scleroderma Dilated capillaries and venules occur not infrequently along the costal margin both in health and disease In elderly persons fine varices or small red or purple spots may appear on the chest The telangiectases are not troublesome no treatment is indicated

One type of telangiectasis is recognized as a definite disease known as familial or hereditary hemorrhagic telangiectasis[416, 417, 418] The condition occurs in both sexes of a family and the trait is transmitted as a Mendelian dominant Multiple telangiectases appear most commonly in the nasal mucosa the tongue lips and cheeks less often on the ears eyelids chest fingers and intestinal mucosa The lesion appears as a small purplish red spot raised or flat with a sharp margin The spot pales but does not fade on pressure There is marked thinning of the walls of the affected vessels which accounts for the tendency to bleed from a slight trauma Epistaxis is a common early symptom of the disease For further details of this disease and its treatment see Oxford Medicine Volume II, Chapter XIX

Another type of telangiectasis which deserves special mention is the so called spider telangiectasis spider nevus, or cutaneous arterial spider According to Bean[419] Erasmus Wilson[420] in 1869 was the first to describe the vascular spider Hanot and Gilbert[421] called attention

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reasons but a satisfactory result is difficult to obtain Tattooing would appear to give the best results

Strawberry nevus, capillary nevus, or capillary hemangioma is a type of nevus found most commonly on the face scalp neck and upper extremities but may occur on other parts of the body It usually is unilateral and appears as a superficial circumscribed lobulated slightly raised bright red tumor which blanches poorly on pressure It is present at birth but may be minute and later grow to several centimeters in diameter and then remain stationary Lister[4 4] observed that strawberry nevi in infants grew more or less rapidly for a few months usually ceased growing between the sixth and eighth months and then retrogressed He reported spontaneous involution in the majority of cases about the fifth year of life The lesion is composed chiefly of venules new vessels form with a lining of large swollen endothelial cells As Ribbert has pointed out the mass of dilated small vessels is supplied by its own artery and vein but has no lateral anastomosis and does not communicate with normal blood vessels in adjacent tissues This type of nevus is a true hemangioma, it responds well to treatment by carbon dioxide snow

Cavernous hemangiomata are found on the face, tongue neck and extremities and in the liver, muscles bones heart kidney stomach intestines brain, and spinal cord In the skin they produce circumscribed or diffuse spongy, lobulated lesions blue or bluish black in color, involving the skin, subcutaneous tissues and often the muscles, the tumors may pulsate The diffuse type may involve an entire extremity They may have their origin in a vascular nevus but usually develop after birth or appear later in life they are not encapsulated and may invade adjacent tissues Rarely, metastases may form, and the tumor may be designated an hemangio endothelioma Cavernous hemangiomata are composed of large blood channels and sinuses lined by endothelium and surrounded by a thin layer of connective tissue Their structure resembles erectile tissue Skin lesions may be treated by injection of a sclerosing solution 5 per cent sodium morrhuate Lesions not responding to injections are treated by radium or surgical excision[4 5] Hemangiomata of the liver may be single or multiple and usually are asymptomatic They may be a cause of hemorrhage from intestines or kidney In bones they are found most commonly in the vertebrae and may be the cause of compression of the spinal cord In the brain hemangiomata are more common below the tentorium than above A combination of lesions in the

to the appearance of vascular spiders in cirrhosis of the liver The cutaneous arterial spider is now known to occur also in pregnancy They are found most commonly on the face, neck, chest, and upper extremities and very rarely on the lower half of the body Eppinger[400] observed vascular spiders only in regions drained by the superior vena cava, but this would not appear to be a factor in determining their localization Lesions develop with greater frequency and in greater numbers in areas exposed to the sun and prone to flushing the face, neck, and upper part of the sternum In hepatic disease, lesions may appear suddenly and persist, or fade slowly or rapidly, an associated palmar flushing often is present They appear between the second and fifth months of pregnancy, persist and even enlarge until their disappearance after delivery and uterine involution[419] The lesion has a central red body, often slightly raised, with fine branching legs often surrounded by an area of erythema The central body may pulsate, its red color fades completely on pressure and quickly reappears with release of pressure This central red body is an arteriole of a parent artery, which is larger than arterioles normally found in the area,[419 4 3] the legs from the central body run parallel to the surface of the skin and appear to be capillaries The wall of the arteriole and parent artery are hypertrophied but no formation of new vessels is evident The vascular spider is not an angioma No treatment is indicated

Vascular Nevi Nevi or birthmarks are of congenital origin In vascular nevi the affected vessels are dilated but formation of new vessels is evident In some, such as the *naevus flammeus* (port-wine stain or birthmark), new vessels conform to a normal pattern (hyperplasia) and communicate with normal vessels in adjacent tissues This type of nevus might be considered a congenital type of telangiectasis It is not a true hemangioma In the so called 'capillary' or 'strawberry nevus the formation of new blood channels is marked, tumor formation rather than hyperplasia is present The lesion is a true hemangioma

Nevus flammeus or nevus vinosus usually is found on one side of the face or on the neck and less frequently on the trunk and extremities, as a flat or slightly raised peripheral red discoloration (port-wine stain) which blanches on pressure leaving a brownish stain behind Its surface is smooth or shows small elevations the color changes with excitement, coughing, or changes in environmental temperature It is present at birth, varies greatly in size but rarely grows after birth This type of nevus is composed of dilated capillaries and venules but there is evidence of hyperplasia of vessels Treatment is only necessary for cosmetic

of the extremities Sympathectomy is followed by temporary relief of the pain but all symptoms disappear after excision of the tumor Slight pain may persist until the wound from the operation has completely healed For further details on glomus tumors see Oxford Medicine Volume II Chapter XIV

PART II

DISEASES OF VEINS

Introduction

The main function of the veins is to return the blood from the capillary system to the heart Disorders of this function may be of cardiac, arterial or venous origin Cardiac insufficiency in the stage of congestive failure is the most common cause of a disturbance in the venous return of blood to the heart If the right ventricle of the heart fails to pump an adequate quantity of blood brought to it by the superior and inferior vena cava the following sequence of events occurs in the systemic veins a slowing of the venous flow and an increase in venous pressure venous stasis and finally edema of the dependent parts of the body Failure of the left ventricle results in similar changes in the pulmonary circulation

An inadequate return of blood to the heart may result in faintness collapse or syncope from cerebral ischemia The cause of these disturbances may be arterial in origin as in postural hypotension[430] or primarily venous as in postural fainting or vasovagal syncope[431] and rapid high acceleration in aircraft In certain individuals a change from the recumbent to the upright position may cause a sudden marked fall of the systolic and diastolic blood pressure followed by complaints of dizziness faintness or even syncope with weakness upon recovery from the attack postural hypotension In these patients the heart rate is unchanged or shows a slight increase as the blood pressure falls sweating extreme pallor and nausea are absent on standing faintness develops when the systolic blood pressure falls to 50 mm Hg Symptoms are prevented or ameliorated by an abdominal binder or binding of the lower extremities The fundamental disturbance in postural hypotension is a loss of reflex vasoconstriction when the subject assumes an upright position due to involvement of the sympathetic nervous system[432] At

cerebellum and in the retina is known as Lindau's disease Surgical excision is the treatment of choice for hemangiomata of muscles and high voltage X-ray therapy for lesions of bones The treatment of lesions of internal organs causing symptoms is palliative

Glomus Tumor Tumors may arise from vessels forming arteriovenous anastomoses or the glomus In 1812, Wood[4, 6] described in detail the clinical picture associated with a glomus tumor and called it a 'painful subcutaneous tubercle The condition attracted little attention until 1924, when Masson[4] showed that the painful nodule or spot was a tumor arising from vessels forming arteriovenous anastomoses Since attention was called to the origin of these painful nodules an increasing number of cases have been reported

Arteriovenous anastomoses forming direct connection between arteries and veins without the intermediation of capillaries are found in different peripheral regions of the body, they are present in large numbers in the palms of the hands and soles of the feet and in even greater numbers at the ends of the fingers and toes Glomus tumors are benign and are found most commonly in the fingers, they usually make their appearance as small, painful reddish purple nodules under the nail or beneath the skin of the finger They usually are single but may be multiple even in the same digit[4, 8] The tumor would appear to be an hypertrophy or overgrowth of the normal glomus It is composed of vessels forming the arteriovenous anastomoses or glomus They are lined by endothelium and surrounded by an abnormal number of glomus cells In some tumors these cells are present in compact sheets, suggesting an epithelial tumor[4, 9] The tumor is surrounded by a collagenous capsule Non-medullated nerve fibers are present in both capsule and tumor

A persistent burning pain is the presenting symptom and may be present for a year or more before the tumor becomes visible Trauma may mark the onset of pain but more often it simply aggravates a preexisting pain In the beginning the pain is localized to the site of the tumor but later it radiates from finger to elbow or to the neck It is aggravated by light touch movement, warmth, and emotional stimuli The affected digit is warmer than the corresponding digit on the normal side, sweating is more marked, the skin is pink or dusky in color and may be thin smooth and shiny, the digit may be smaller than normal[4, 8] The findings are similar to those observed in the so-called reflex dystrophy of the extremity,[148] but osteoporosis is absent However a similar mechanism would appear to be responsible for the burning pain and the vasodilation in glomus tumors as in post traumatic painful disorders

structive and nonobstructive venous disorders of local origin As the veins are thin walled and compared to the arteries have a small amount of elastic and muscle tissue it is not surprising that a mechanical obstruction of a large vein should result in dilatation This is found most commonly in the superficial veins of the lower extremity (varix or varicose veins) in the pampiniform plexus of spermatic veins (varicocele) and in the superior and inferior hemorrhoidal veins of the rectum and anus (hemorrhoids) An hereditary weakness of the walls of the veins in these areas would appear to be the primary cause of the dilatation

Phlebosclerosis (Phlebofibrosis)

Phlebosclerosis occurs as a disseminated lesion in young adults usually males between twenty and forty years of age, without an associated arteriosclerosis[434] The condition affects small veins in different parts of the body but chiefly the superficial veins of both legs It causes thickening of the walls of the veins with narrowing of the lumen but no venous obstruction or other symptoms The affected veins feel like small hard smooth cords not adherent to adjacent tissues According to Hauswirth and Eisenberg[435] the earliest histological change is a loss of endothelium and hyalinization of the denuded surface of the intima Later there is a marked hyperplasia of the connective tissue, more marked in the media than intima with no development of fatty degeneration or calcification They found similar lesions in the vaso vasorum The cause of the condition is unknown but would appear to be of little clinical importance

Varix or Varicose Veins

The term varix or varicose veins is applied to a dilated and tortuous condition of the superficial veins of the lower extremities, which lie between the skin and deep fascia of the limb The primary change would appear to be a dilatation of the vein followed by incompetency of its valves After a temporary dilatation a vein may return to normal size but once a permanent dilatation is established an incompetency of the valves of the superficial veins results The vein becomes longer and tortuous and segments of it tend to bulge immediately below each valve, a state of varicosity is established Later incompetency of the valves of the communicating veins particularly in the lower third of the leg, is prone to develop

tacks of faintness or vasovagal syncope may occur in healthy individuals as a result of prolonged standing as in watching a parade, in patients assuming the upright position after rest in bed from an infection or protracted illness or in patients with 'effort syndrome' In this type of postural fainting the heart rate usually is slowed, the diastolic pressure shows little change and faintness develops when the blood pressure falls below 90 mm Hg in contrast to 50 mm Hg in postural hypotension sweating, marked pallor, and nausea usually are present The pressure exerted on the veins by the abdominal and skeletal muscles is an important factor in overcoming the effects of gravity on the venous return from the lower half of the body Relaxation of the skeletal muscles while standing still or lack of tone and weakness of the abdominal and skeletal muscles from fatigue or ill health may result in stasis of blood in the veins below the level of the heart and cause an inadequate return of blood to the heart Weiss and his associates[433] have reproduced the clinical manifestations of postural fainting by the administration of sodium nitrite and have shown that circulatory collapse induced by sodium nitrite is due primarily to a decrease in venous tone These authors are of the opinion that the functional weakness or circulatory collapse is a disproportion between the total volume of blood and total volume of the vascular beds in the splanchnic area and in the lower extremity For further details on postural hypotension and vasovagal syncope the reader is referred to the original articles and the section on Syncope and Related Syndromes in Oxford Medicine

Primary disorders of the veins apart from postural fainting or vasovagal syncope, are seldom the cause of a general disturance of the circulation They tend to affect the venous return from one or more organs or parts of the body The common causes of these local disturbances are (1) intrinsic obstruction of a large vein from thrombosis or new growth, (2) extrinsic obstruction due to pressure from a gravid uterus new growth, scar tissue or increased abdominal pressure, (3) obstruction of interhepatic branches of portal veins in portal cirrhosis (4) primary dilatation of veins from the effect of gravity or straining or both, as in primary varicose veins Diseases of the veins, therefore, may be divided into two main groups (1) non-obstructive and ( ) obstructive

Nonobstructive Venous Disturbances

Dilatation of the veins or phlebectasia is a usual finding in both ob

and remained until the patient took a few steps when it rapidly disappeared into the deep system of veins

Smirk[440] demonstrated that active muscular exercise of the legs in normal subjects diminished the venous pressure in the superficial veins Pollock *et al*[436] studied the effect of walking on the venous pressure at the ankle in normal subjects and in patients with varicose veins and incompetent valves They found that walking decreased the mean venous pressure of 86 millimeters of mercury on standing still to [illegible] millimeters in normal subjects and from 81 millimeters to 44 millimeters of mercury in patients with incompetent valves On cessation of the exercise the venous pressure returned to the standing or hydrostatic level in normal subjects in an average time of 31 seconds and in patients with incompetent venous valves in [illegible]8 seconds It is evident from these observations that incompetent valves at the saphenofemoral opening and in the long saphenous vein are responsible for the rapid return of venous pressure in muscular relaxation in patients with varicose veins The incompetent valves are unable to prevent the reverse flow of blood from the femoral vein into the long saphenous vein on muscular relaxation

Structural changes in varicose veins first consist of hypertrophy of the media and later degeneration and atrophy of the muscular and elastic tissues with connective tissue proliferation and perivascular fibrosis The veins may become adherent to surrounding tissues and skin In older patients calcification of the walls of the veins may develop thrombi may form particularly in areas where the veins bulge, old thrombi may become calcified and form phleboliths Thrombosed varicose veins are rarely the source of emboli

The early complaints apart from the unsightly appearance of dilated tortuous veins are a sense of fatigue and heaviness or fullness of the legs after prolonged standing or strenuous exercise Cramp like pains at night may occur but are less common than in arterial insufficiency Edema and cyanosis are absent Chapman and Asmussen[441] have suggested that pooling of blood in varicose veins may be a cause of undue fatigue, shortness of breath fainting and precordial distress A localized thrombosis often the result of trauma, is a common occurrence in primary varicose veins A segment of a dilated vein usually below the knee, becomes red and tender The thrombophlebitis usually subsides and remains localized, but the thrombosis may extend upwards to the saphenofemoral opening it rarely if ever extends into the femoral vein and becomes a source of emboli Recurring attacks of localized throm

Varicose veins may develop spontaneously (primary varicose veins) or they may develop distal to an obstruction of a large vein (secondary varicose veins). It is generally agreed that primary varicose veins develop in individuals with an inherited weakness of the wall of the superficial veins and possibly a congenital defect of the valves. They may be found in adolescents but usually develop in the third to sixth decades of life; women are more commonly affected than men. Allen *et al*[13] obtained a family history of varicose veins in 62 per cent of cases. Varicose veins are not the result of infections.[413] They may result from extrinsic pressure of a mass on the iliac vein or inferior vena cava but are usually associated with occupations requiring prolonged standing and/or with increased intra-abdominal tension due to lifting, straining, coughing, or a gravid uterus, or are considered a late manifestation of thrombosis of the deep veins of the extremity. As the deep veins do not develop varicosities it is evident that lack of muscular support and muscular pressure on the superficial veins and the impairment of the elasticity of the skin in older individuals favor the development of a permanent dilatation. It seems clear that the fundamental cause of dilatation and incompetency of the valves of the superficial veins is the increased pressure resulting from standing and increased intra-abdominal tension. Different observers have measured the pressure in the long saphenous vein and have found that the pressure in both normal and varicose veins, with the limb immobile, closely corresponds with the calculated hydrostatic pressure of a column of blood extending from the level of the right atrium of the heart to the ankle. Pollack *et al*[436] found that the average venous pressure at the ankle was 7.2 millimeters of mercury in the recumbent position, 52 millimeters sitting and 81.9 millimeters standing. McPheeters *et al*[437] and Adams[438] demonstrated the increase in venous pressure from increased intra-abdominal tension. Adams found that one sudden strain produced a marked increase of pressure in a dilated saphenous vein with incompetent valves but that a sustained effort was required to produce a maximal increase of pressure if the dilated vein had competent valves. Trendelenburg[439] showed and McPheeters *et al*[437] confirmed by the injection of lipiodol that the flow of blood is outward from the femoral vein and downward in the long saphenous in the standing position if the valves at the saphenofemoral opening and in the long saphenous vein are incompetent. McPheeters found that lipiodol injected at the upper end of the dilated long saphenous vein rapidly appeared in the superficial veins of the leg

phenous vein The efficiency of the valves in the long and short saphenous veins may be determined by the Brodie[444]-Trendelenburg[439] test The patient lies down with the lower extremity elevated high until the superficial veins have emptied by gravity A bandage is applied to the middle of the thigh tight enough to constrict the superficial veins but not the deep veins, and the patient stands erect If the saphenous vein above the bandage fills rapidly it is evidence of a downward flow of blood from the femoral and of valvular incompetence in the saphenous vein If on release of the bandage, the long saphenous vein below the bandage fills rapidly from above, the valves in the long saphenous vein below the bandage are incompetent If after the release of the bandage the veins below remain collapsed and empty for twenty to thirty seconds this is an indication that the communicating veins are competent but if they fill in five to fifteen seconds there is incompetence of valves in some communicating veins of the leg and in the short saphenous vein Valvular incompetency of the short saphenous vein may be confirmed by repeating the Brodie Trendelenburg test with the thumb compressing the short saphenous vein in the popliteal space If the thumb but not the bandage is removed when the patient stands erect, and the veins of the leg fill rapidly there is incompetence of the short as well as the long saphenous vein

A careful history and physical examination will usually lead to the diagnosis or exclusion of an extrinsic obstruction or a congenital or acquired arteriovenous fistula as a cause of dilated and varicose veins in the extremity

The differential diagnosis of conditions causing a chronic ulceration of the leg may be a more difficult problem Other causes of induration and ulceration from venous insufficiency are thrombosis of the deep veins (the postthrombotic or postphlebitic syndrome) and an arteriovenous fistula An antecedent history of a swollen leg after a pregnancy surgical operation or fracture of the extremity with the subsequent development, months or years later of chronic edema induration and ulceration on the inner side of the leg above the ankle points to thrombosis of the deep veins as the cause Varicose veins and ulceration in one leg developing after a penetrating injury of the extremity should suggest an acquired arteriovenous fistula

Chronic ulcers of the leg not due to venous insufficiency occur in obliterative arterial disease, syphilis and erythema induratum (Bazin's disease) Indolent ulcers of the leg in chronic obliterative arterial dis

bosis are common. In patients with extensive or long standing primary varicose veins who have to stand or do muscular work in the erect position for long hours nutritional changes, the result of venous stasis, tend to develop in the skin and subcutaneous tissue of the lower third of the leg on the inner side above the internal malleolus. Trauma and an incompetent communicating vein would appear to be localizing factors. The earliest sign is edema above the ankle. At first the edema disappears with rest in bed at night but later it is present in the morning and persists unless the patient rests in a recumbent position for a longer time. Moderate congestion and cyanosis of the skin is associated with the edema. Later manifestations in the affected area are pigmentation, brawny induration, and ulceration. Anoxia of the tissues favors the escape of erythrocytes from the minute vessels and the development of areas of brown pigmentation which may be diffuse in venous insufficiency of long standing. Itching or a burning sensation is often a troublesome symptom and may be the first manifestation of a chronic scaling or weeping eczema. Scratching to relieve the itching causes small abrasions and bleeding which contribute to the pigmentation of the skin. The skin and subcutaneous tissues become thickened and hard (brawny induration) due to an inflammatory reaction from edema fluid and low grade infection. A local tissue hypersensitivity may be partially responsible for the induration. After an injury, even a minor one, in the affected area an ulcer develops which heals but tends to recur and enlarge in the same area and become secondarily infected. An inflamed ulcer is painful, particularly one in the region of the saphenous nerve. Chronic varicose ulcer is the common cause of serious disability from varicose veins.

Zimmerman,[44] contrary to prevailing opinion, believes that the cutaneous changes in the lower third of the leg are not the result of venous stasis but are of inflammatory origin arising by direct extension from infection within the varicosities. He gives no convincing proof of the presence of infection in the wall of the varicose vein in the affected area, and Edwards[443] was unable to stain or culture bacteria from the clot or wall of varicose veins.

Varicose veins are easily diagnosed if the patient is thin and the lower extremity is examined with the patient in an upright position. In obese individuals, a dilated long saphenous vein seldom is visible but can be detected by careful palpation. A round swelling which gives an impulse on coughing may be present over the upper end of the long sa-

in the long saphenous vein with valvular incompetence dilates tributaries of the vein increases the work of the deep veins and accelerates the development of venous insufficiency resulting in ulceration of the leg the object of treatment is to remove or obliterate the incompetent superficial varicose veins and incompetent communicating veins beneath the ulcer Until recently the generally accepted method of treatment in the past thirty years has been the ligation of the long saphenous vein flush with the femoral junction and obliteration of the incompetent superficial veins by the injection of sclerosing solutions The great advantage of the injection method of treatment elaborated by Sicard *et al*[446] in Europe and McPheeters[447] in North America was that it caused little interruption in the daily routine of the patient However experience has shown that recurrences are frequent due to incomplete obliteration by the injection treatment and to recanalization of thrombosed veins following the injection of sclerosing solutions At the present time on this continent the generally accepted method of treatment is resection of the long saphenous vein flush with the femoral junction division and ligation of all tributaries in the area total removal by stripping and incision of the long and the short saphenous veins if both are involved and ligation of incompetent communicating veins Injection treatment is usually reserved for varicosities not removed at operation or dilated collateral veins forming after the stripping operation The chief contraindications to the radical treatment of varicose veins are congestive heart failure, malignancy systemic infections, severe blood diseases renal insufficiency uncontrolled diabetes mellitus coexisting obliterative arterial disease of the extremity, or a recent inflammatory reaction of the leg In secondary varicose veins it is of little value to undertake a stripping operation unless the primary cause of the venous obstruction can be relieved

When an ulcer is present and acutely inflamed, surgical and injection treatment should be preceded by a period of rest in bed with the leg elevated and the application of warm compresses of Dakin s solution in a dilution of one in twelve or one in six several times a day until the acute inflammation has subsided and the ulcer is clean If the patient is unable to interrupt his daily work, ambulatory treatment of the ulcer by the foam rubber pad and compression bandage method described by Nobl[448] and McPheeters[449] is an effective method of preliminary treatment Marked induration and large chronic ulcers may require more radical treatment (See post thrombotic ulceration p 506 (184))

ease are uncommon and when present are associated with similar lesions of the toes and foot Trauma from hot water bottles or mechanical injury is the usual cause Hines and Farber[11] have described, under the term 'hypertensive ischemic ulcers,' a rare form of painful ulceration of the lateral or posterior surface of the calf occurring in patients with a diastolic hypertension, most frequently in women fifty to seventy years of age The lesion would appear to result from ischemia due to sclerosis of the cutaneous arterioles Syphilitic ulceration begins as a painless nodule or group of nodules in the subcutaneous tissue or skin, which enlarge and break down discharging a gummy fluid and leaving a deep ulcer, often serpiginous, showing little tendency to spontaneous cure They are found more often on the lateral and posterior surface of the leg The Wassermann test usually is positive Erythema induration occurs in young women, the lesions are symmetrical and usually on the back of the legs

Treatment Patients presenting the first sign of dilatation or local varicosities of the superficial veins and even young individuals with only a family history of varicose veins should be advised concerning the deleterious effect of occupations which require standing for long periods of time or the lifting of heavy weights, and the need for such persons to rest with the lower extremities elevated They should realize the importance of taking regular physical exercise out of doors for the maintenance of general health and tone of the skeletal and abdominal muscles Controlled rest and exercise should be prescribed during pregnancy or any prolonged illness in bed Methods of treatment depend on the severity of the involvement of the superficial veins, the presence of induration or ulceration of the lower leg, the age and economic status of the patient All patients with varicose veins should avoid standing for long periods without rest, lifting heavy weights, straining and strenuous exercise When resting in the sitting position, the legs should be elevated Patients should be cautioned against the danger of mechanical thermal or chemical trauma to the lower third of the leg In patients with a minor involvement of the superficial veins, active treatment may be restricted to the wearing of an elastic stocking during the day but the patient should be warned that this may not prevent the progress of the condition and he should be re-examined every few months

If the valves of the saphenous veins are incompetent, with or without chronic edema, induration, or ulceration of the lower third of the leg, more radical treatment is indicated As the retrograde flow of blood

distressing pain, the condition should be treated by ligation and resection or by the injection of sclerosing solution to one third of the veins If primary varicocele is the condition preventing a recruit from joining the armed forces, operation is advisable

In secondary varicocele, the successful removal of the proximal venous obstruction relieves the condition

Hemorrhoids

Hemorrhoids or piles are varicose dilatations involving the hemorrhoidal plexus of veins There are two varieties (1) internal hemorrhoids which have their origin above the anorectal line from the superior hemorrhoidal plexus of veins and are covered by mucous membrane (2) external hemorrhoids which arise below the anorectal line from the inferior hemorrhoidal plexus and are covered by skin A combination of internal and external hemorrhoids is often present

An hereditary weakness of the veins is the probable essential cause of hemorrhoids Congestion of the hemorrhoidal veins is the important predisposing factor in internal and interno external hemorrhoids The common causes of congestion are (1) straining from heavy lifting or at stool due to constipation or diarrhea from the use of cathartics or from disease or from a chronic cough, enlarged prostate or stricture, (2) increased intra abdominal pressure from new growth or a gravid uterus Portal engorgement from congestive heart failure or cirrhosis of the liver is a rare cause of hemorrhoids Infection of the skin with phlebitis is considered a predisposing cause of external hemorrhoids

Internal hemorrhoids are the most common variety and the most troublesome They may be classified as to location and severity In first degree internal hemorrhoids only seen on proctoscopic examination of the rectum they appear as soft purplish nodules or masses in the right anterior right posterior and left lateral quadrants of the rectum and often with smaller nodules between the quadrants They are usually asymptomatic but bleeding on defecation may be present Second degree hemorrhoids protrude into the anal canal on excessive straining but retract spontaneously into the rectum after straining Third degree hemorrhoids protrude with minimal straining and remain protruded until replaced into the rectum by digital pressure Fourth degree hemorrhoids tend to remain prolapsed outside the anus despite repeated digital replacement Bleeding and prolapse are the common signs of internal hemorrhoids Bleeding occurs at defecation and the fresh red blood

Varicocele

Varicocele is a dilated and tortuous condition of the veins forming the pampiniform plexus Primary varicocele the more common form occurs in young adults and nearly always on the left side (over 90 per cent of cases) Secondary varicocele results from pressure on one or other of the spermatic veins at the pelvi rectal region by carcinoma at the kidney level by new growths of either kidney, and less often by retroperitoneal growths

The cause of primary varicocele is obscure but a congenital weakness of the veins probably plays a part The different course of the left and right spermatic veins appears to afford a satisfactory explanation for the greater frequency of primary varicocele on the left side The right spermatic vein enters the inferior vena cava obliquely in the direction of the venous return, the left spermatic vein opens at right angles into the left renal vein and, in addition, may be compressed at the brim of the pelvis by a sigmoid colon loaded with feces Normally the left testicle is lower and the left spermatic vein longer than on the right side

Primary varicocele usually causes little or no local discomfort After exercise such as riding, particularly in warm weather, a sense of fullness and a dragging or aching pain may be present in a pendulous scrotum More often primary varicocele is a cause of mental distress in young adults They are often nervous and have the unwarranted fear that the varicocele may cause impotence or be the result of masturbation

The condition is easily recognized on palpation, the distended tortuous veins in the lax or pendulous scrotum give the sensation likened to a bag of worms The swelling enlarges on standing, coughing or straining and tends to disappear when the patient lies down The left testicle may be smaller than the right A rapidly developing right or left varicocele is an indication of a proximal obstruction of the spermatic vein secondary varicocele The common cause is a renal tumor The urine should be examined for blood and the abdomen for a renal or retroperitoneal tumor

Treatment A young patient with primary varicocele should be assured that the condition is not a serious one and will not result in impotence He should be advised to control any tendency to constipation and to take regular outdoor exercise Older individuals with a large varicocele should be advised to wear a scrotal suspensory If the varicocele is large and interferes with exercise or sitting or is the cause of

or strangulated the patient should be at rest in bed with the buttocks on a pillow and the foot of the bed raised An attempt should be made to reduce the prolapsed inflamed hemorrhoids Compresses moistened with hot boracic acid or Dakin s solution should be applied firmly to the anus and changed every four hours Treatment should be continued until the acute condition subsides, when radical treatment by injection ligature or excision of the hemorrhoids is indicated For details of treatment by injection or operation the reader is referred to standard textbooks of surgery

External hemorrhoids result from dilatation of the network of venules and small veins at the margin of the anus superficial to the external sphincter They are covered by skin and tend to radiate in longitudinal folds from the anus With straining the folds of the skin become bluish in color and turgid External hemorrhoids tend to become thrombosed from the effects of chronic constipation, pregnancy physical effort, or direct trauma A purplish swelling appears and the vein is firm, tender and painful The patient may be unable to sit or walk in comfort for one to three days when the pain usually subsides After healing a tag of skin with central fibrous core is left Tags of skin resulting from attacks of thrombosis make proper cleansing of the anal region difficult and give rise to local irritation and itching Apart from thrombosis and its after effects external hemorrhoids cause no symptoms

The treatment of external hemorrhoids consists of control of constipation by regular bowel habits, with a mild laxative when necessary and proper cleansing of the anal region after defecation The immediate treatment of a painful thrombosed pile is rest in bed, the opening of the bowels by warm oil enemata and the application of moist hot compresses for the relief of pain If the pain is very severe a few drops of novocain should be injected and the clot removed through an incision made over the thrombosed hemorrhoid Tags of skin should be removed For severe itching Barker[150] recommends an ointment of beta cocaine 1 0 menthol 0 dissolved in olive oil and mixed with 10 grams of lanolin

Obstructive Venous Disturbances

Thrombosis and Phlebitis

Thrombosis of veins (the partial or complete occlusion of veins by a thrombus) and phlebitis (inflammation of veins) are associated so frequently that the two processes and the resulting disturbances often are

is unmixed with the feces The hemorrhage may be excessive but is usually small in amount and recurrent, it may be the cause of a definite anemia from loss of blood Prolapse is the chief cause of discomfort Constriction of the prolapsed hemorrhoid by the sphincter ani is a cause of severe pain and often strangulation resulting in thrombosis of the dilated vein and ischemic ulceration and even gangrene At this stage infection is a frequent complication resulting in cellular infiltration of tissues and ulceration An internal hemorrhoid consists of dilated venules and veins surrounded by a fibrous stroma covered by columnar epithelium After recurrent prolapse the vein contains old and recent thrombi and some are converted into fibrous cords There is an increased fibrosis of stroma and thickening of the mucous membrane At this stage bleeding is decreased or absent

The diagnosis of internal hemorrhoids is suggested by a history of rectal bleeding of fresh blood unmixed with feces or of a mass coming down during defecation A proctoscopic examination is necessary for a definite diagnosis of first degree internal hemorrhoids but, if the patient is asked to bear down and traction made on the margin of the anus they often may be brought into view A rectal examination with the finger should be made in old cases of rectal bleeding as an aid in the diagnosis of the cause of bleeding

Treatment The treatment of internal hemorrhoids should include not only the local treatment but also control by appropriate measures or removal of the primary cause of congestion of the superior hemorrhoidal veins If the primary cause can be removed or controlled, local palliative treatment of second or third degree hemorrhoids may clear them up or relieve the discomfort The control of constipation is most important Strong laxatives must be avoided The bowels should be regulated by mild laxatives such as senna or mineral oil Occasional rectal injection of olive oil may be necessary As a spastic type of constipation is usually present, the patient should have a non irritating diet Soft paper or absorbent cotton should be used after defecation the anal orifice thoroughly cleansed with warm water and a lanolin ointment applied to prevent infection Protruding hemorrhoids should be sponged with cold water and gently replaced by the finger A suppository containing extract of hamamelis or an anusol suppository (iodresorcino sulphate of bismuth zinc oxide and balsam of Peru) should be introduced into the lower rectum night and morning for a month Anemia due to loss of blood should be treated by adequate daily doses of iron If the hemorrhoid remains prolapsed after defecation and becomes inflamed

blood stream A mixed thrombus greyish red in color and composed of platelets and fibrin makes up the intermediate portion of the thrombus between the head and tail A red thrombus may be short or it may extend proximally 30 or 40 centimeters into a larger vein A second white thrombus may form proximal to the primary red thrombus and be superimposed by another red thrombus For further details on the formation and structure of thrombi the reader is referred to Aschoff and standard textbooks on pathology

Although the mechanism of the formation of thrombi is not clearly defined there is general agreement that the agglutination of platelets is an early and an essential phase of the process There are four established factors which favor the deposition of platelets and formation of thrombi (1) changes in the intima of the vein ( ) changes in the blood flow (slowing and eddying of the blood stream), (3) changes in the blood platelets conducive to agglutination coagulation and clot retraction (4) changes in the blood plasma accelerating coagulation A local histological change in the intima of a vein from infection or trauma is the inciting factor in determining the deposition of platelets and the site of origin of a thrombus secondary to phlebitis—*secondary or phlebitic thrombosis* Any one of the other three factors mentioned may play the principal role in causing a *spontaneous venous thrombosis*, but no one factor acting alone is responsible for the deposition of platelets and the formation of a thrombus

Spontaneous Venous Thrombosis (Phlebothrombosis) Spontaneous venous thrombi have their origin most often in the veins of the lower extremity Extensive examination of the veins of the lower extremity by Rossle,[45] Neumann,[453] Frykolm[454] Hunter *et al*,[455] and McLachlin and Paterson[456] have shown that venous thrombi are present in 27 to 60 per cent of routine autopsies on adults over twenty years of age The most serious complication of venous thrombosis is pulmonary embolism In 567 consecutive autopsies at the Toronto General Hospital, Belt[457] found pulmonary emboli in 56 cases (10 per cent), and in 37 cases (6 5 per cent) the emboli were of sufficient bulk to occlude two thirds of the pulmonary circulation and therefore[458] were regarded as the immediate cause of death Hunter *et al*[4 5] found an incidence of pulmonary embolism of 14 per cent in routine autopsies and pulmonary embolism the immediate causeof death in 3 13 per cent of cases Belt s autopsy findings also showed that the incidence of pulmonary embolism was higher in medical than surgical patients confined to bed and higher among patients with cardiac failure These observations have been confirmed by

referred to under the term 'thrombophlebitis' Another reason for the use of this combined term has been a prevailing conception that phlebitis from injury of the wall of a vein by infection, trauma, or degeneration was the primary and essential cause of the formation of a thrombus Although phlebitis frequently gives rise to the local formation of a thrombus—*secondary or phlebitic thrombosis*—it is well known that a thrombus may form without any change in the wall of a vein demonstrable by standard methods of examination—*primary or spontaneous enous thrombosis* It is probably true that a thrombus developing in an apparently normal vein may be followed by local changes in the wall of the vein where the thrombus is adherent and the condition may be considered a *thrombophlebitis* However, it is also true that a thrombus in spontaneous venous thrombosis is not as firmly attached to the wall of the vein as a thrombus in phlebitic thrombosis and, for this reason a spontaneous thrombus is the usual origin of a fatal pulmonary embolus Further, the clinical course and complications differ in primary and secondary venous thrombosis and present different problems in treatment The two processes, thrombosis and phlebitis and these two types of venous thrombosis require separate consideration

Thrombosis A thrombus may be defined as a solid mass or plug formed in the living heart or vessels from constituents of the blood[151] *Thrombi form in the streaming movement of the blood* In this respect the process of thrombosis differs from the intravascular clotting of blood that occurs after death with the circulation at a standstill In contrast with the soft, elastic red or chicken-fat post mortem clot, a thrombus at least the head or primary portion is firm inelastic, white or greyish in color, and unlike a post mortem clot, adheres to the wall of the vessel at its site of origin The beginning of a thrombus is an agglutination of platelets deposited in transverse ridges on the wall of the vein Later the ridges are surrounded by leucocytes they increase in size and number by the accumulation of platelets and leucocytes With the liberation of thromboplastin from this platelet mass, fibrin threads form between the ridges, entangling red blood cells The platelet mass enlarges until the lumen of the vein is partially or, more often, completely occluded With complete occlusion of the vein, the blood becomes stagnant up to the entrance of the next tributary vein and clots forming the red part or tail of the thrombus which consists chiefly of fibrin and red blood cells In appearance and structure a red thrombus resembles a blood clot, it is more friable than the primary white portion and its proximal part in the beginning is not adherent to the wall of the vein but waves free in the

are the common source of emboli causing non fatal pulmonary infarction and are rarely the cause of a sudden fatal pulmonary embolism Neumann has suggested that there are two clinical types of venous thrombosis one, occurring in younger persons, having its origin in the plantar veins, rapidly progressing upwards and the source of a massive pulmonary embolism, and the other occurring in older individuals beginning in the veins of the calf slowly progressive, and tending to be the origin of multiple non fatal pulmonary emboli Frykolm[454] believes that thrombi begin in muscle veins of calf and/or adductor muscles of thigh and grow into a larger vein From his phlebographic studies on living surgical patients Bauer[403] who regards venous thrombosis as an acute process has concluded that in 98 per cent of cases the thrombus begins in a muscle vein of the calf and grows into one of the larger veins of the lower leg forming a deposition thrombus which enlarges upwards in the direction of the venous flow and gradually occludes the vein and becomes attached to the vessel wall In 80 per cent of his cases this stage was followed by the building up of a red or coagulation thrombus extending upwards and partially filling the femoral vein for a period of twenty-four to forty eight hours During this period the red thrombus may break off in whole or in part and give rise to a pulmonary embolism or, more commonly continue to grow in thickness filling the lumen of the femoral vein Later the thrombus becomes attached to the wall of the femoral vein along the entire length and produces a typical phlegmasia alba dolens The phlebographic studies of Bauer support the conclusion drawn from pathological and clinical observations that the usual site of origin of venous thrombi causing pulmonary embolism or phlegmasia alba dolens is in the veins below the knee The autopsy findings of Rossle Neumann and Frykolm and the clinical investigations of Homans do not support the conclusion of Bauer that there is a longitudinal growth of the primary thrombus in the vein of the leg into the femoral vein, with the development of typical phlegmasia alba dolens in 80 per cent of cases of venous thrombosis in surgical patients and this high incidence is not in accord with clinical experience Homans[401] has suggested that in some instances a thrombus in a calf vein may be propagated upwards into the femoral vein becoming adherent to the wall in one part and partially occluding the vein without giving rise to signs and symptoms of phlegmasia alba dolens

In 100 routine autopsies on medical male patients over forty years of age dying in a Veterans Hospital McLachlin and Paterson[456] removed the veins in continuity from the lower end of the inferior vena cava to

others.[459,460] The seriousness of pulmonary embolism as a complication of venous thrombosis depends on the size of the embolus or emboli and the pre-existing state of the heart and pulmonary circulation. If a single large embolus or multiple smaller emboli lodging within a few hours occlude the trunk of the pulmonary artery or both main branches the occlusion causes acute pulmonary edema and death usually occurs in minutes or a few hours. More often smaller non-fatal emboli lodge in the peripheral branches of a pulmonary artery. If the venous return from the lungs is impeded,[461] as in mitral stenosis and congestive heart failure the embolus produces an infarction. Still smaller emboli may lodge in small peripheral branches of a pulmonary artery and cause no recognizable signs or symptoms.

It is generally agreed that in over 80 per cent of cases the veins of the lower extremity are the site of origin of thrombi causing pulmonary embolism. Other sites of origin of emboli in a relatively small percentage of cases are the pelvic veins and the right heart in certain cardiac patients. Aschoff observed that an embolus occluding the trunk or both main branches of the pulmonary artery consisted of blood clots 35 to 45 centimeters in length with an average thickness corresponding to the width of the femoral vein. He came to the conclusion that a fatal pulmonary embolism could only arise from a long medium sized vein like the femoral and believed that the thrombus had its origin in the femoral vein usually in a valve pocket and was propagated distally. Recent and more extensive dissections of the veins of the lower extremity in patients dying of medical and surgical conditions,[45, 453, 454, 455] the clinical and pathological investigations of Homans,[46] and the phlebographic studies of Bauer[463] provide evidence that the common sites of origin of venous thrombi are in veins below the knee, the plantar veins, deep veins of the calf, and tributary veins in muscles of the calf. All are agreed that venous thrombi are propagated in the direction of the venous flow toward the heart and not distally. Homans, Rossle, and Neumann are in agreement with Aschoff that a pulmonary embolism causing sudden death comes from a thrombus in a vein the size of the femoral but contend that its origin is usually in a vein below the knee, that it is propagated upwards and is seldom primary in the femoral vein. In two fatal cases of massive pulmonary embolism, Homans[46] found thrombosis of muscle veins in the calf and in the posterior tibial and popliteal veins, and an embolus in the lung consisting of a long coagulation thrombus which evidently had its origin in the femoral vein. Rossle[45] and Neumann[4 3] consider that thrombi arising in the veins of the calf

embolism in medical patients is a recurrent and seldom a single event and is usually a contributing cause of death in patients with congestive heart failure The very complete dissections of the larger veins of the lower extremities by McLachlin and Paterson demonstrate that thrombi may have their origin in veins above or below the knee the thrombi are usually short, and more than one thrombus may be present in the same vein From the histological examination of thrombi in elderly patients inactive or confined to bed it is evident that venous thrombosis tends to be a slowly progressive process and often an additive process The thrombi are the source of small usually multiple pulmonary emboli which may be a contributing cause of death but are seldom the primary cause

The much higher incidence of venous thrombosis than pulmonary embolism found by all workers is a clear indication that bland thrombi may be present in the veins of the lower extremity without producing pulmonary emboli or local signs and symptoms and should be considered as a third clinical type of venous thrombosis In a consideration of the etiology of spontaneous venous thrombosis it is important from the standpoint of diagnosis and treatment to consider the conditions and factors that may influence or determine the development and the clinical course and complications of the different clinical types of venous thrombosis

As has been mentioned, the factors known to favor the deposition of platelets and the formation of a thrombus are (1) changes in the intima of the vein ( ) changes in blood flow (slowing and eddying of the blood stream), (3) changes in the blood platelets conducive to agglutination, coagulation and clot retraction and (4) changes in the blood accelerating coagulation There is general agreement that spontaneous venous thrombosis is not preceded by a local injury of the wall of the vein that can be demonstrated by standard methods of histological examination Recently Samuels[46] using a technique devised by O Neill[468] for the observation of the living endothelium of veins has studied the inception of thrombosis in the veins of dogs following mechanical and chemical injuries producing no demonstrable anatomical change in the endothelial cells He found that the earliest change was a deposition of platelets along the intercellular cement line At the point of injury the platelets increased in number metamorphosed and coalesced forming a platelet thrombus this was soon followed by a deposit of fibrin over the platelet thrombus Chambers and Zweifach[469] found that an increase in the acidity or a decrease in the calcium content of a

the posterior tibial at the level of the internal malleolus, opened the veins and determined the location of thrombi They also searched the pulmonary arteries and their branches for emboli, using the 'open book method recommended by Belt[465] Bland thrombi were found in 34 per cent of cases at the following sites pelvic veins only, 2, thigh and pelvic veins, 1, thigh veins 17, thigh and leg veins, 10, leg veins only, 4 The plantar veins were not examined The 34 cases had 76 distinct thrombi with the following distribution pelvic veins, 6, thigh veins, 49, and leg veins, 21 Multiple thrombi were found in one or more veins in 19 of the 34 cases, of these 15 were bilateral They were unilateral in 19 cases 14 on the right side and 5 on the left The majority of the thrombi were short and in none of the cases did a red thrombus extend upwards from a vein in the lower leg and fill the lumen of the femoral vein Pulmonary emboli were present in 56 per cent of the 34 cases The emboli were multiple in 75 per cent and produced infarction in 40 per cent, but no massive pulmonary embolism is recorded They found no significant difference in the incidence of venous thrombosis in patients from forty to over eighty years of age but the incidence of pulmonary embolism was significantly higher in patients over fifty years of age In 135 autopsies, the majority on elderly patients, Raeburn[466] found thrombosis of the veins in one or both legs in 35 cases (26 9 per cent) Fifty-four per cent of the thrombi showed histological evidence of recurrent thrombosis, some showed three sequences of thrombosis and organization Raeburn advances the thesis that in most instances venous thrombosis in the leg is a chronic additive process and not an acute and progressive process

The autopsy findings of McLachlin and Paterson and Raeburn in older medical patients and the phlebographic studies of Bauer on living surgical patients support the conception advanced by Neumann of two types of spontaneous venous thrombosis one slowly progressive and the other rapidly progressive, and are in accord with the different clinical courses of pulmonary embolism in medical and post-operative patients It has been well established that unsuspected sudden death from a massive pulmonary embolism usually occurs after a surgical operation, less often following parturition and is a rare occurrence in medical patients In surgical and obstetrical patients thrombosis tends to be an acute process the thrombus has its origin in a vein below the knee probably in a plantar or muscle vein, is rapidly propagated into the femoral as a red or coagulation thrombus which becomes the source of a massive pulmonary embolus As pointed out by Belt[4 7] pulmonary

observations indicate that slowing of the venous flow increases the incidence of venous thrombosis and pulmonary embolism and that the incidence of pulmonary infarction is lower in postoperative patients exercised in bed and allowed up and encouraged to move about soon after the operation

At present there is no direct proof that slowing of the venous flow causes an alteration in the intercellular cement and initiates thrombosis but there is indirect evidence Rossle[43] and Frykolm[474] believe that collapse of veins in the muscles of the calf and adductor muscles of the thigh from pressure of the mattress and slowing of the circulation in patients confined to bed initiates thrombosis in muscle veins and that this platelet thrombus grows into a larger vein Frykolm has advanced the idea that collapse of the muscle veins from pressure and slowing of the circulation produces a nutritional injury of the intima giving rise to a deposition of platelets This conception is supported by Samuels[487] experimental findings He found that moderate distension of a vein decreases and collapse increases the deposition of platelets at the point of injury

A factor considered to be a contributory cause of venous thrombosis in certain conditions is an increase in the number and stickiness or adhesiveness of the platelets After major surgical operations[476 477 478] and parturition,[477 478] it has been shown that a rise in the number of platelets occurs about the fourth day after operation or delivery, reaching a maximum about the tenth day, with a return to the initial level between the fourteenth and twenty fourth day Dawbarn *et al*[477] concluded that the rise in the number of platelets after surgical operations and parturition was a physiological response of the bone marrow from the absorption of unknown breakdown products from tissue injury Wright[479] devised a method for measuring quantitatively the stickiness of platelets and found that the increase in circulatory platelets after operation and parturition was associated with an increased stickiness of the platelets beginning at the fourth day and becoming maximum about the tenth day[478] From these findings it is evident that in a given case the stimulus causing the increase in the number of platelets is also the cause of the increased stickiness Moolten *et al*[480] confirmed Wright's observations and also found a greater stickiness of the platelets following compound fractures of the leg and peptic ulcer with massive hemorrhage and a persistent stickiness of the platelets with a normal or slightly elevated count in cancer patients not subjected to a surgical operation This finding in cancer patients indicates that it is due to a qualitative change

perfusate altered the physical state of the interendothelial cement, increasing its adhesiveness to carbon particles From these observations it seems evident that the earliest change in the wall of a vein favoring deposition of platelets is not an obvious anatomical change in the endothelium, as in secondary or phlebitic thrombosis, but an alteration in the physical state of the intercellular cement resulting in an increased adhesiveness of the cement substance

If one accepts an alteration in the physical state of the intercullula cement as the primary change in the wall of the vein in spontaneous thrombosis, the cause of the altered state of the cement substance must be related to conditions and factors predisposing to the formation of thrombi It has been definitely established that confinement to bed and congestive heart failure are the two most important conditions predisposing to the development of venous thrombosis and pulmonary embolism Of the known factors favoring thrombus formation, slowing of the venous flow would appear to play the dominant role under these conditions Hunter *et al* [4] found that the incidence of venous thrombosis, determined by dissection of veins of the lower extremity in fatal cases, was 53 07 per cent in patients not exercised in bed and non-ambulatory, and 17 9 per cent in patients exercised in bed or ambulatory up to forty-eight hours before death Belt's[457] autopsy findings demonstrated the high incidence of spontaneous venous thrombosis in cases of congestive heart failure and the high correlation between heart failure and pulmonary embolism Since the time of Virchow it has been recognized that slowing but not cessation of the venous flow is essential for the formation of a platelet thrombus Blumgart and Weiss[4 0] have shown that the venous flow in the general circulation is slower than normal in cardiac insufficiency Wright *et al*,[4 1] using radioactive Na^{24}, measured the rate of venous flow from the ankle to the groin in surgical patients before and after operation In surgical patients confined to bed they found a progressive decrease in the rate of flow beginning the third day after operation and becoming most marked at the tenth to twelfth day Maximal slowing developed at the time pulmonary embolism usually occurs after a surgical operation Different observers[47 4 3 4 4] have found a decreased incidence of pulmonary embolism following the institution of remedial exercises in bed and of early rising from bed after operation Wright *et al*[471] found no apparent slowing of the venous flow in patients ambulatory from the third day after operation Wright and Osborn[475] also found that dorsal and plantar flexion of the foot in a recumbent patient doubled the venous flow rate The above

Wright[48] in rabbits showed that dicumarol decreased the adhesiveness of platelets but that there was no significant alteration in their number. From the above findings it seems evident that the adhesiveness and the *deposition and agglutination of platelets are closely related phenomena* in the initiation of thrombus formation and that heparin and dicumarol reduce the adhesiveness of platelets and prevent the formation of a white thrombus.

When the accumulation of platelets in an initial white thrombus completely interrupts the flow of blood in the vein, the blood column up to the entrance of the next tributary vein and in some instances beyond it, clots and forms a red or coagulation thrombus. After the adhesion and accumulation of platelets in a vein, alterations in the platelets occur with the liberation of the platelet factor in thromboplastin generation essential for the clotting of blood and clot retraction. With the generation of thromboplastin from platelets and from plasma factors, thromboplastin converts prothrombin to thrombin, fibrinogen is converted *to fibrin by thrombin and a superimposed coagulation thrombus* is formed. In certain cases tissue juice from local trauma in the leg may be an additional source of thromboplastin and accelerate the thrombotic process.

As has been pointed out, the formation of a venous thrombus may be a slow and limited process in elderly patients inactive or confined to bed before death and a more rapid and progressive process in certain patients following parturition, major surgical operations, extensive trauma, or a massive hemorrhage. It seems evident that the factors favoring the deposition and rate of accumulation of platelets in a white thrombus are also factors affecting the rate of development and length of the superimposed coagulation thrombus. It would seem reasonable to suppose that conditions having the reverse effect of heparin and dicu*marol on the platelets and plasma would act as precipitating factors in* initiating the formation of a white thrombus and affect the rate of its development, and also affect the rate of formation and propagation of the coagulation thrombus. At present there is no convincing evidence that the results of tests of various plasma factors in the coagulation process are of value in detecting a tendency to venous thrombosis.

Signs and Symptoms. The signs and symptoms of thrombosis of veins of the lower extremity depend on the rate of development, the extent and the stage of the thrombotic process. The early signs and symptoms usually mentioned in postoperative venous thrombosis are pain (soreness or tightness) in the calf on movement of the leg, discomfort in the

in the platelets It seems probable that the persistence of this change is due to the continued stimulation of the bone marrow by breakdown products of cancer tissue Wright proved that the increased stickiness of the platelets was not related to the erythrocyte sedimentation rate and presented evidence from observations on postoperative patients[478] and experimental thrombocytosis[491] in rabbits that the increased stickiness of platelets was due to the presence in the blood of a larger proportion of new platelets which had been released from the bone marrow in response to tissue injury

As platelets form the origin of a thrombus and play an essential part in the formation of a red or coagulation thrombus, it seems reasonable to conclude that increased stickiness of platelets would accelerate the deposition of platelets on the intima of the vein if the venous flow was slowed by rest in bed, and that an increase in the number of platelets would accelerate the formation of a white thrombus and, later, the formation and propagation of a coagulation thrombus

It is generally recognized that physiochemical changes in the blood plasma and in the platelets must play a role in causing venous thrombosis but the nature and significance of the changes favoring the initial deposit of platelets on the intima in a slowly moving or eddying blood stream and the later formation of a superimposed red or coagulation thrombus have not been clearly defined Chambers and Zweibach[479] have presented evidence to suggest that chemical changes in the blood increase the adhesiveness of the intercellular cement of the intima and thereby favor the initial deposition of platelets Best *et al* [48] and Solandt and Best [483] have demonstrated experimentally in animals that the administration of an adequate amount of the anticoagulant heparin prevents the deposition of platelets and the formation of a white or agglutination thrombus Solandt and Best[494] have shown that platelet agglutination in their experimental animals is continuous with smaller doses of heparin than that required to prevent the deposition of platelets even though the clotting time is prolonged to six hours or longer Wright[479] tested the in vitro effect of different anticoagulants—heparin sodium oxalate and chlorazol dyes—on the adhesiveness of platelets She found that the adhesiveness of platelets in normal human blood was decreased by the different anticoagulants and that the degree of adhesiveness was inversely proportional to the concentration of anticoagulant present Dale and Jaques[48] found that dicumarol delayed or prevented the formation of an agglutination thrombus in animals and its effect paralleled the reduction in prothrombin activity Spooner and Meyer,[486] in humans, and

and Counseller[489] found that clinical signs and symptoms of femoral thrombosis were observed in only five patients Among surgical patients carefully examined for local signs and symptoms of venous thrombosis, Farmer and Smithwick[490] report sudden death from pulmonary embolism following operation in ten of twelve patients in whom thrombo embolic disease had not been suspected previously In a similar survey by Wigginton *et al* [491] they found that all of the seven sudden deaths from pulmonary embolism occurred in patients without a previously recognized vascular lesion

Acute femoro iliac venous thrombosis of the clinical type causing pain and marked swelling of the extremity phlegmasia alba dolens usually occurs in younger women confined to bed after childbirth and following typhoid fever It occurs less often following minor surgical operations in older individuals and rarely in patients confined to bed with debilitating disorders Fatal pulmonary embolism is a rare complication and the source of the embolism is the femoral vein of the other leg which had shown no recognizable clinical signs and symptoms of venous thrombosis In a case of fatal pulmonary embolism Barker and Counsellor[489] found the thrombus intact in the iliac and femoral veins of the swollen leg and a fresh thrombus in the femoral and iliac veins of the other apparently normal extremity Dissection of veins has shown that venous thrombosis is bilateral in over 40 per cent of cases In postpartum thrombosis the patient complains of the sudden onset of pain, often severe, in the groin inner side of thigh or back of the calf and the leg becomes markedly swollen from the ankle to the groin within the first twenty four hours after the onset of pain The pain and swelling are preceded by a moderate rise in temperature and pulse rate Tenderness in Scarpa s triangle is usually present In a few instances pulsations in the femoral artery are diminished or absent The superficial veins are dilated

During convalescence from typhoid fever, Conner[49] observed signs and symptoms of venous thrombosis in the calf or foot in 10 per cent of cases Marked swelling of the affected extremity was not a common symptom When present it appeared two to three days or as long as three weeks after the onset of local signs in the leg Signs and symptoms of recurrent pulmonary infarction were present in 0 04 per cent of convalescent typhoid fever cases In two thirds of these cases the embolic attacks occurred before local signs or symptoms of venous thrombosis were observed in the leg After typhoid fever femoro iliac thrombosis would appear to be a less acute process than in postpartum cases

calf on forcible dorsiflexion of the foot (Homan's sign), deep tenderness on palpation of the calf and, less often, the sole of the foot, increased firmness of tissues in the area of tenderness, and varying degrees of swelling of ankle and leg or of the whole limb from ankle to groin These signs and symptoms should be considered as presumptive evidence of the presence of venous thrombosis and not the basis for a positive diagnosis of thrombosis of the deep veins of the leg Bauer,[463c] who has called attention to the importance of these signs and symptoms in the early diagnosis of venous thrombosis, has stated that in one third to one half of surgical patients with deep tenderness and mild swelling of the calf and spontaneous pain the veins of the leg have been found free of thrombosis when examined by phlebography, and none of them subsequently developed symptoms of venous thrombosis The most important diagnostic signs and symptoms of the presence of venous thrombosis in a lower extremity are the signs and symptoms of pulmonary embolism a complication of venous thrombosis, or pain and marked swelling of the limb from ankle to groin characteristic of one type of acute femoro-iliac thrombosis phlegmasia alba dolens

The symptoms and signs of pulmonary embolism depend on the size of the embolism A massive pulmonary embolism may occur after a major surgical operation or parturition and usually results in death in a few minutes or a few hours The common clinical manifestations are the sudden onset of extreme shortness of breath, a substernal constricting pain a fall in blood pressure tachycardia cyanosis and shock Small emboli are more common than a large embolus or emboli causing sudden death They may cause no symptoms or may result in a pulmonary infarction characterized by an attack of pleural pain, shortness of breath less often cough and hemoptysis, and a moderate fever Multiple attacks of pulmonary infarction from recurring emboli of moderate size are common and are a contributing cause of death in patients with myocardial insufficiency The association of symptoms of pulmonary infarction and early suggestive local signs and symptoms of venous thrombosis in the leg justifies a positive diagnosis of venous thrombosis On the other hand the absence of these local signs and symptoms is of little value in excluding the presence of venous thrombosis, for in at least 80 per cent of cases of fatal pulmonary embolism local signs and symptoms are absent In an analysis of 161 cases of fatal pulmonary embolism Zilliacus[488] found that 135 of the deaths occurred without local signs of venous thrombosis and 26 after previous signs of thrombosis In a summary of 116 postoperative cases of fatal pulmonary embolism Barker

manifestations of phlegmasia cerulea dolens were present at the onset in 56 per cent of cases and in 44 per cent the onset was preceded by a few days to a couple of weeks by the clinical manifestations of phlegmasia alba dolens The local signs and symptoms are the sudden onset of pain in calf or foot and cyanosis of the entire extremity with maximum intensity in the toes and heel, followed by marked swelling of the extremity which may extend beyond the groin Arterial pulsations are often diminished or absent When gangrene is present, it develops four to eight days after the onset of cyanosis Dissections at autopsy have shown an extensive thrombosis completely occluding the large veins of the extremity and their tributary veins but the arterial tree has been found free of organic occlusions Their patency has been confirmed by arteriography Haimovici states that the walls of the veins show phlebitic changes of varying intensity and a diffuse inflammatory infiltration of the adventitia which may extend to the adventitia of adjacent arteries and explain the associated arterial spasm present in some of the cases Phlegmasia cerulea dolens occurs in the same conditions that phlegmasia alba dolens is prone to develop, but may occur in the upper extremity The cause of the superficial gangrene of the toes is evidently of venous and not arterial origin and results from the extensive obstruction to the venous return from the leg

In the usual clinical type of acute femoral or femoro iliac venous thrombosis following major surgical operations fractures and trauma pain and visible swelling of the extremity are absent and suggestive local signs and symptoms of thrombosis of veins below the knee are also absent in many cases The first indication of a venous thrombosis is only too often sudden death from a massive pulmonary embolism during an uneventful convalescence from a major surgical operation [180] In this type of acute venous thrombosis the superimposed coagulation thrombus in the femoral vein does not occlude the vein completely due to retraction of the clot following the disintegration of platelets As the thrombus does not fill the lumen of the vein and is not adherent to the wall at this stage it tends to break off in whole or in part and produces a fatal massive pulmonary embolism

Diagnosis The early diagnosis of a spontaneous thrombosis of the large veins of the leg and thigh is a difficult problem and a positive diagnosis from local signs and symptoms probably is impossible Positive diagnostic clinical manifestations of a venous thrombosis are a unilateral swelling from ankle to groin in conditions known to cause a phlegmasia alba dolens or the occurrence of signs and symptoms of pulmonary in

The pain in phlegmasia alba dolens would appear to be due to ischemia. An essential factor in the causation of the marked edema in these cases would appear to be a complete occlusion of the femoral and iliac veins by a thrombus. In experimental animals, Zimmerman and de Takats[493] have shown that perivenous inflammation or obstruction of the lymphatics is not the cause of the rapid initial swelling of the limb. The complete occlusion of the femoral and iliac veins by a thrombus propagated from the deep veins of the calf would appear to be due to increased sympathetic vasoconstriction. DeBakey *et al*[494] showed, in animals that a local chemical phlebitis produced a marked diminution in the volume of peripheral pulsations in the foot and that this effect could be abolished by local infiltration with procaine at the site of the chemical phlebitis or by resection of the lumbar sympathetic ganglia and chain. In patients with phlegmasia alba dolens, Ochsner and DeBakey[49] observed a prompt relief of pain and return of normal temperature with a disappearance of marked edema in eight to twelve days following procaine block of the regional sympathetic ganglia. In the opinion of Ochsner and DeBakey, the factors causing the edema are increased venous pressure from the thrombosis, increased permeability of the capillaries due to capillary stasis and diminution in flow of lymph as a result of diminished arterial pulsations.[496a, b] The relatively sudden onset of pain and swelling of the extremity in postpartum phlegmasia alba dolens, the diminution or absence of pulsations in the femoral artery in certain patients, and the favorable effect on pain, edema, and fever following procaine block of the lumbar ganglia support the conclusion that increased sympathetic vasoconstriction of arteries, arterioles, and veins is primarily responsible for the complete occlusion of the femoral and iliac veins by a recent thrombus and the resulting disturbances in the normal exchange of intravascular and extravascular fluids in the extremity. It seems clear that the origin of the stimulus resulting in increased sympathetic vasoconstriction is related to the affected vein and the thrombotic process. In the light of the experimental findings of DeBakey *et al*,[494] the presence of tenderness in Scarpa's triangle in association with pain and swelling of the extremity suggests that a perivenous tissue reaction is the cause of the tenderness and the origin of the stimulus.

A rare form of acute femoro-iliac venous thrombosis, phlegmasia cerulea dolens or blue thrombophlebitis, is characterized by pain, marked cyanosis and swelling of the entire extremity and by superficial gangrene of the toes. From a review of the clinical and pathological information on cases reported and cases studied Haimovici[497] found that clinical

much less common in young adults than in middle aged or elderly persons Hunter *et al*[4] found at autopsy an incidence of venous thrombosis of 5 6 per cent in patients over forty years of age confined to bed from illness for more than a brief period before death The incidence of pulmonary embolism in the thrombosis cases was 5 3 per cent of which 4 8 per cent were fatal and 20 5 per cent non fatal pulmonary emboli In this study, venous thrombosis of the extremities was present in 50 per cent of patients confined to bed pulmonary embolism was present in 25 per cent of the thrombosed cases and absent in 75 per cent In a more complete dissection of the veins of the lower extremity in a similar group of cases McLachlin and Paterson[10] found that the incidence of venous thrombosis was 34 per cent and that 56 per cent of the thrombosed cases had single or recurrent small pulmonary emboli in 44 per cent pulmonary emboli were absent In 85 per cent of the thrombosed cases the thrombi were short and in about 50 per cent emboli were not present in the lungs In 15 per cent of the thrombosed cases the thrombus had extended from the deep veins of the calf into the femoral vein and a unilateral edema of the ankle and leg was present The thrombus was organized and adhered to the wall of the vein with the exception of a short coagulation thrombus in the femoral which was present in 40 per cent of the cases with edema These investigations indicate that in older patients confined to bed for different disorders one may expect a venous thrombosis of the extremities to be present in one third to one half with recurrent small pulmonary emboli as a complication in 25 to 50 per cent and edema of the leg as a sequela of venous thrombosis in about 15 per cent It also seems clear that the thrombotic process is slowly progressive with minor exacerbations resulting in small recurrent pulmonary emboli in about 50 per cent of the thrombosed cases

The high incidence of pulmonary embolism in patients with congestive heart failure is now generally recognized At autopsy on twenty five patients dying of chronic congestive heart failure Belt[1] found multiple emboli causing pulmonary infarction in 9 per cent and in 60 per cent the emboli causing infarction had occluded two thirds of the pulmonary circulation and were considered the immediate cause of death In no instance was a single massive pulmonary embolism a cause of sudden death as may occur in postoperative thrombosis with embolism In 60 per cent of the cases the origin of the emboli was in the veins of the lower extremity and local manifestations of venous thrombosis or insufficiency were usually absent In fatal cases of mitral stenosis with

farction or massive pulmonary embolism Soreness or tightness of the calf on movement, tenderness on deep palpation of the calf, local firmness of the tissues of the calf, discomfort in the calf on dorsiflexion of the foot, and minor swelling often only determined by daily measurement of the calf are suggestive early local signs and symptoms of venous thrombosis of the deep veins of the calf, but occurring alone they should not be considered the basis for a positive diagnosis Allen *et al*,[498] who examined the limbs for early local signs of venous thrombosis following operation, found signs and symptoms of pulmonary embolism the first indication of venous thrombosis in 41 per cent of cases In a statistical study of 343 cases of postoperative fatal pulmonary embolus by Barker *et al*,[499] there was no clinical evidence of venous thrombosis in 45 per cent, but thrombi were found in the veins at autopsy

Signs and symptoms of pulmonary infarction occurring alone or in association with suggestive local signs and symptoms of venous thrombosis justify a positive diagnosis of thrombosis of the deep veins of the leg Unfortunately pulmonary and leg clinical manifestations are absent in the majority of surgical cases of rapidly progressing venous thrombosis causing sudden death from a massive pulmonary embolism[488, 489, 490, 491] In cases of this type an unexplained rise in temperature and pulse rate occurring in an apparently normal convalescence from a surgical operation may be the only evidence suggestive of venous thrombosis Bauer,[463] DeBakey *et al*,[500] and others advocate phlebography as a means of establishing an early diagnosis of acute venous thrombosis Allen *et al*[498] found the interpretation of phlebograms difficult and the results of phlebography uncertain This method of diagnosis is now being employed less and less

Clinical course The clinical course of venous thrombosis of the extremities depends on the age of the patient, the conditions and factors predisposing to its development, and the rate of development and extent of the thrombotic process The natural course of the thrombotic process is often cut short by a pulmonary embolism or emboli which may be a primary or contributing cause of death In patients not dying of pulmonary embolism or other causes thrombotic occlusions of the large veins of the lower extremities are the cause of varying degrees of chronic venous insufficiency characterized by edema, pigmentation, brawny induration, and, less frequently, ulcertation of the lower portion of the leg—the postphlebitic or postthrombotic syndrome

Venous thrombosis and its complication pulmonary embolism, are

the edema fluid causes a proliferation of the subcutaneous connective tissue which eventually impairs lymphatic drainage The common clinical manifestations are edema and heaviness and easy fatigue in the calf which may occur with or without exercise

In the first year after an acute postpartum thrombosis the edema feeling of heaviness and easy fatigue tend to lessen in severity or to disappear but in the next five years many patients have a return of exacerbation of pre existing symptoms often accompanied by an aching or bursting pain in the calf which develops after prolonged standing and is relieved by rest and elevation of the extremity At this stage an area of persistent edema of skin and subcutaneous tissues, warm to the touch and suggestive of a low grade inflammation frequently develops on the inner side of the leg above the ankle and becomes indurated[504] (brawny induration), minute hemorrhages occur resulting in a brown pigmentation of the skin Later the affected area tends to ulcerate Early ulcers heal with rest and elevation of the limb but tend to recur after minimal trauma and heal more slowly In a follow up examination of patients with postpartum venous thrombosis treated by prolonged immobilization Hojensgard[0] found that only 11 per cent remained symptom free and that 89 per cent developed serious sequelae of venous thrombosis heaviness and fatigue and edema in over 80 per cent induration in 35 per cent and ulceration in 27 per cent Forty five per cent had to wear a bandage or elastic stocking all the time

Edema induration and ulceration are also sequelae following post operative acute thrombosis of the deep veins of the calf, the femoral and/or the iliac veins not accompanied by visible swelling of the extremity Homans[504] was among the first to point out that induration and ulceration of the lower leg often occurred in the absence of varicosity of the long and short saphenous veins By clinical and pathological observation he was able to show that in many instances, they were not sequelae of primary varicose veins (varicose ulcer) but the result of an earlier thrombosis of the deep veins of the extremity with or without swelling of the extremity, a condition now known as the postthrombotic or postphlebitic syndrome Bauer[403] is of the opinion that 80 to 90 per cent of so called varicose ulcers are sequels to acute deep vein thromboses of the lower extremity

After a postoperative or postpartum acute femoral or femoro iliac venous thrombosis the venous return from the extremity is through collateral venous channels in the muscles of the calf and thigh and the superficial veins If the patient does not die from pulmonary embolism

congestive failure, Levine and White[501] found pulmonary infarction in 61 per cent In middle-aged and elderly medical patients confined to bed with different disorders it would appear that the incidence of venous thrombosis varies from 34 to 50 per cent and that the probable mortality from recurrent small pulmonary emboli in thrombosed cases varies from 5 to as high as 60 per cent in patients with chronic congestive heart failure

In acute femoro iliac venous thrombosis without swelling of the extremity in postoperative patients, the incidence of fatal pulmonary embolism is much higher than in acute femoro-iliac thrombosis accompanied by swelling of the entire extremity following parturition Robertson[0?] reported a postoperative case mortality from pulmonary embolism of 0 7 per cent In a statistical study of 172,888 patients operated upon at the Mayo Clinic before 1940, Barker *et al*[503] reported an incidence of 0 92 per cent of venous thrombosis, 0 52 per cent of pulmonary embolism and 0 20 per cent of fatal pulmonary embolism Among the 1665 cases of venous thrombosis, the incidence of pulmonary embolism was about 50 per cent and the fatality rate from pulmonary embolism 20 per cent From a similar study in Europe, Bauer[463b] reported that among 2 874 cases of postoperative venous thrombosis the fatality rate from pulmonary embolism was 16 6 per cent, and among 1 603 cases of postpartum thrombosis the fatality rate from pulmonary embolism was 3 6 per cent It seems evident that the probable mortality from pulmonary embolism in acute femoral or femoro iliac thrombosis is five times higher in patients without visible swelling of the leg than in patients with marked swelling of the entire extremity Sudden death from a single large pulmonary embolism may occur in both postoperative and postpartum cases but the origin of the large embolus in postpartum cases is not from veins of the swollen extremity, it is from the femoral vein of the apparently normal extremity,[464 489] which is also the usual finding in cases of sudden death from embolism following operation[490]

In patients with phlegmasia alba dolens not dying of pulmonary embolism or other causes the edema of the extremity may subside in a week or two or persist for several weeks depending mainly on the treatment prescribed If the edema subsides within a couple of weeks and due care is taken after the patient is up and about a slight swelling of the ankle on prolonged standing may be the only evidence of the impaired venous circulation If the initial edema does not subside completely or recurs after the patient is ambulatory, the increased protein content of

phlegmasia alba dolens Induration and ulceration may develop in five ten or more years following an earlier acute venous thrombosis of the deep veins of the lower extremity Bauer reports a 72 per cent incidence of induration and a 52 per cent incidence of chronic ulceration of the lower leg

A varicose ulcer and a postthrombotic ulcer occur at the same site and it is important in treatment to differentiate an ulcer secondary to primary varicose veins from one secondary to a thrombosis of the deep veins of the extremity In the latter, significant dilatation and varicosity of the short and long saphenous veins are often absent, induration of the skin and fibrosis of the floor of the ulcer and infection are more marked ulcers tend to be larger, run a more chronic course and show a tendency to recur after treatment effective in varicose ulcers

Prevention of Venous Thrombosis and Pulmonary Embolism Prevention is more important than the treatment of pulmonary embolism and venous thrombosis Apart from a relatively small percentage of cases in which the origin of an embolus may be the pelvic veins or the right side of the heart the prevention of venous thrombosis in the large veins of the lower extremities means the prevention of pulmonary embolism

Methods of treatment at present advocated for the prevention of venous thrombosis in the lower extremities and its complication pulmonary embolism are (1) therapeutic measures chiefly aimed to improve or accelerate the venous return from the lower extremities to the heart and to improve the pulmonary circulation ( ) prevention of thrombus formation in the extremities or the formation of new thrombi on established thrombi by the use of anticoagulants, (3) bilateral ligation and division of the superficial femoral or a more proximal vein for the prevention of pulmonary embolism

Pathological and clinical observations clearly demonstrate that confinement to bed with muscular relaxation and decreased muscular activity of the lower limbs resulting in a slowing of the venous return to the heart is the most important condition favoring the development of venous thrombosis Myocardial insufficiency is the cause of slowing of venous flow in the general circulation, and by impeding the venous return from the lungs favors the production of infarcts from smaller emboli Its importance should be recognized and appropriate treatment prescribed The chief local causes of slowing of the venous return from the lower extremities are increased intra abdominal pressure from different causes immobilization of the extremity with fractures pressure

or other cause in the acute stage, organization of the white and the coagulation parts of the thrombus occurs In phlegmasia alba dolens both the white and coagulation parts of the thrombus completely fill the lumen of the femoral and iliac veins due to the associated increased vasoconstriction In acute femoral or femoro iliac thrombosis without visible swelling of the leg, the distal white thrombus fills the lumen of the vein but the proximal superimposed coagulation thrombus only partially fills the lumen due to retraction of the clot As organization of the thrombus develops the proximal part of the thrombus becomes adherent only to part of the wall of the femoral vein leaving a free channel at the side Where the thrombus becomes adherent to the wall of the vein, a non-infective thrombophlebitis is established but the wall of the vein in the early stages of organization shows no significant changes in the majority of cases[4 6 4] Histological changes may be no greater than in non thrombosed veins of the same patient[08] The thrombotic process destroys the valves of the large thrombosed veins of the extremity[0] Later, canalization of the thrombus occurs and phlebitic changes become more marked The incompetency of the valves of the large thrombosed veins only too often results in dilation and incompetency of the communication veins with or without incompetency of the long and short saphenous veins, and the onset of the postthrombotic syndrome This would appear to be due to a sustained venous pressure while walking The incompetency of the valves in the deep veins within the fascial sheath permits a back-flow of blood with every relaxation of the muscles in walking In individuals whose occupations require them to stand for prolonged periods of time, this back flow from the deep veins results in dilatation and later incompetency of the valves of collateral venous channels and still later, of the short and long saphenous veins Pollock *et al*[436] found that walking decreased the mean venous pressure at the ankle on quiet standing from 86 to 22 millimeters of mercury in normal subjects, and from 87 to only 76 millimeters in patients having a previous femoro iliac thrombosis The higher venous pressure on standing which is maintained in walking results in the development of persistent edema, induration, and ulceration of the lower leg Linton[508] considers this ambulatory venous hypertension the chief etiological factor in the production of the postthrombotic syndrome

The clinical manifestations and the clinical course of the postthrombotic syndrome following an acute venous thrombosis of the deep veins without visible swelling of the extremity are the same as following

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on muscles of the calf and thigh from a hard mattress, and confinement to bed Wright *et al*[471] measured the rate of venous flow from ankle to groin before and after delivery in pregnancy, the removal of masses from the pelvis and paracentesis in ascites, and found that the venous flow rate was significantly slower and increased after pressure was relieved The alleviation and prevention of increased intra abdominal pressure is important therefore, in the prevention of venous thrombosis Masses causing extrinsic pressure on the veins of the pelvis should be removed Tight bandages which restrict the movement of the diaphragm and the abdominal muscles or undue pressure on the muscles of the calf and thigh from a hard mattress in bed or on the operating table should be avoided The effect of confinement to bed and muscular inactivity on the incidence of venous thrombosis and pulmonary embolism has been demonstrated by autopsy dissection of veins Among middle-aged and elderly patients suffering from different disorders and confined to bed for more than a brief period before death, it has been shown that venous thrombi are present in the calf and thigh in one third to one half the cases, and that one-quarter to one half of the thrombosed cases have had recurrent pulmonary emboli The autopsy findings of Hunter *et al*[4] indicate that exercise in bed or ambulation up to forty eight hours before death decreased the incidence of venous thrombosis 35 per cent It has been shown that active muscular movement of patients at rest increases the rate of venous flow Smith and Allen[509] observed that two minutes of rapid active movement of the leg while a patient was in the supine position immediately increased the venous flow Wright and Osborne[4 5] found that two minutes of vigorous dorsal and plantar flexion of the foot doubled the rate of venous flow from ankle to groin Remedial exercises in bed and early rising from bed after surgical operation and parturition have been advocated for a long time for the prevention or amelioration of surgical complications, but until recent years complete bed rest has been the usual postoperative treatment From the studies of Leithauser[10] and Blodgett and Beattie[511] it is evident that early ambulation is a safe procedure in the majority of surgical patients and that it improves the well being of the patient From a controlled study of early rising and walking, Blodgett and Beattie concluded that early ambulation tends to maintain the patient s strength lessens pain in wounds reduces the incidence of wound disruption and infection and the incidence of pulmonary atelectasis, and shortens the length of the patient's stay in hospital but does not reduce the incidence of phlebitis and venous thrombosis The authors do not

record any sudden deaths from massive pulmonary embolism in the early rising or control series of 681 patients and only two deaths from pulmonary infarction one of a patient ambulatory the first day after operation suggesting the presence of a venous thrombosis prior to operation and one of a patient confined to bed The number is too small to permit a conclusion on the effect of early or late rising in the prevention of embolism Jorpes[4] in Sweden and Canavarro[4 3] in the United States have reported a 50 per cent decrease in the incidence of thrombo embolism following the early institution of remedial exercises in bed and early rising from bed after operations Power[4 4] found that the fatality rate from pulmonary embolism was twice as great in patients confined to bed for an average of twelve days after a major surgical operation as in patients treated by ambulation in the first few days after operation but the incidence of venous thrombosis and non fatal pulmonary embolism was not decreased He states that fatalities from massive pulmonary embolism are less common than they were before the revival of early postoperative ambulation As sudden death from massive pulmonary embolism usually occurs without signs and symptoms of venous thrombosis in the lower extremities[490 491 5 4] the lower incidence suggests that early rising and walking after operations retards the development of acute femoral venous thrombosis The observation that early ambulation after operation does not reduce the incidence of venous thrombosis or the incidence of non fatal pulmonary embolism cannot be accepted as proof that early ambulation after operation does not retard the development of venous thrombosis If older patients are confined to bed for more than a brief period before operation autopsy dissection of veins indicates that venous thrombosis would be present prior to operation in one third[4 6] to one half[455] the patients and it is in this type of venous thrombosis that recurrent non fatal pulmonary emboli usually occur If remedial exercises in bed and early ambulation prevent or retard the development of venous thrombosis as the observations of Power on massive pulmonary embolism suggest and the autopsy findings of Hunter *et al* indicate the systematic application of these preventive measures in patients confined to bed for different disorders should lessen not only the incidence of fatal pulmonary embolism but also the incidence of the late sequelae from venous thrombosis

Recently Wilkins and Stanton[51] have recommended the wearing of elastic stockings as an additional measure for the prevention of pulmonary embolism In a controlled study on a large series of medical surgical and obstetrical hospital patients over twenty years of age, they

found that the wearing of elastic stockings reduced by one half the expected incidence of fatal pulmonary embolism

Patients requiring an operation should be kept up and about if possible and given adequate fluids prior to operation After operation or childbirth, the body and extremities should be kept warm to prevent vasoconstriction from cooling of the body or the direct effect of cold on the limbs If the patient cannot assume the recumbent position in bed full flexion of the thighs on the abdomen should be avoided and the lower extremities kept as straight as possible The foot of the bed should be raised about six inches whenever possible and the thighs and calves should be protected from undue pressure from the mattress If the patient's condition requires that he be confined to bed daily passive and active exercises of the legs and feet and breathing exercises should be prescribed Straining produces a sudden increase in venous pressure which favors the dislodgement of an embolus from a recent thrombus It is important therefore to prevent attacks of coughing and undue straining on the bed pan and on urination If the patient's condition permits ambulatory treatment should begin in the first three days after operation or childbirth following the plan of Leithauser [510] The treatment outlined for surgical and obstetrical patients in bed should be carried out with medical patients confined to bed for different disorders if their condition permits

Conditions which may produce alterations in the constituents of the blood and predispose to thrombosis if slowing of the venous flow is present are dehydration anemia, and trauma Loss of body fluids and electrolytes from sweating vomiting diarrhea or hemorrhage should be prevented or controlled by appropriate measures Patients with severe anemia from hemorrhage should be given blood transfusion At operation care should be taken to avoid any unnecessary injury of tissues and thereby lessen the effect of increased stickiness of the platelets as a predisposing factor in thrombosis If it can be avoided, tissues and veins of the lower extremities should not be used for treatments by injection

In 1936 Murray Best and their associates [13] proved that the intravenous injection of purified heparin prolongs clotting time and effectively prevents the formation of thrombi in veins of dogs traumatized by mechanical and chemical means Two years later they reported[314] that none of 315 postoperative patients receiving heparin by a continuous intravenous drip developed evidence of pulmonary embolism or venous thrombosis Their results in the prophylactic use of heparin were

confirmed by Crafoord in collaboration with Jorpes[1] and by Bauer[473] in Sweden It has been shown that heparin will not dissolve a pre-existing thrombus but will prevent its extension and further thrombo embolic complications and prevent new thrombus formation if the clotting time is prolonged to fifteen minutes i e two to three times the normal clotting time The effect of heparin is manifest within a few minutes after the injection but the effect disappears in about an hour after stopping the administration of the drug by a continuous intravenous drip According to Murray[16] the only contraindication to the use of heparin is an active bleeding vessel For the prophylaxis of venous thrombosis and its thrombo embolic complications Murray[17] recommends the intravenous injection of heparin as a continuous drip 200,000 units or 200 milligrams of heparin are added to 1000 cubic centimeters of saline or saline and glucose The injection is started at a rate of about 30 drops per minute Clotting time determinations are done every two or three hours, when it reaches fifteen minutes or twice to three times the normal, the rate of injection is decreased to 20 drops per minute or according to the effect on the clotting time In postoperative patients the administration of heparin is continued for a period of seven to fourteen days the clotting time being checked twice a day after the first twenty four hours

Crafoord[515b] found the continuous intravenous drip method impracticable and replaced it by repeated intravenous injections of heparin in a 5 per cent sterile solution Crafoord and Jorpes[1] recommend an intravenous injection of 50 to 70 milligrams of heparin at four hourly intervals during the day and a night dose of 100 to 125 milligrams The first injection is given four hours after the operation and the treatment continued over a period of five to ten days No daily estimations of the clotting time are made Among 325 patients given prophylactic treatment with heparin there were no undesirable reactions and not a single instance of thrombo embolism occurred Swedish workers generally have found the repeated intravenous injections of heparin, without daily estimations of the clotting time a safe and effective method of administration of the drug When treatment was started four hours after an operation bleeding in the operation field had not been a problem If bleeding occurs it can be controlled promptly by the intravenous injection of 50 to 100 milligrams of protamine sulphate in a 1 per cent solution

In 1941 Link and his associates[518] isolated and synthesized the hemorrhagic agent in the sweet clover disease observed and described by

Schofield.[569] This anticoagulant, now called dicumarol, interferes with the synthesis of prothrombin in the liver and impairs coagulation of the blood by lowering the concentration of prothrombin in the blood. The level of prothrombin in the blood may be determined by the Quick[570] one stage prothrombin test which is used as a guide for the safe administration of dicumarol. The normal prothrombin time by the Quick test depends on the activity of the thromboplastin used in the test and may vary from twelve to twenty-five seconds. For this reason, Hurn *et al*[571] have recommended that results of the Quick prothrombin test be reported not in seconds but in percentages of prothrombin concentration in the blood. They describe a method by which the prothrombin time for different preparations of thromboplastin may be converted to percentages of prothrombin in the blood. According to the technique of the Quick test used at the Mayo Clinic,[5] the normal prothrombin time is seventeen to nineteen seconds; a prothrombin time of twenty seven seconds signifies 30 per cent prothrombin, thirty five seconds, 20 per cent prothrombin, and fifty-eight seconds, 10 per cent prothrombin. Dicumarol is non toxic and is administered by mouth but its anticoagulant effect does not become evident for thirty-six hours or longer and may persist for six to ten days after its administration has been discontinued. This prolonged effect is increased in hepatic and renal insufficiency. Experience has shown that the effect on the prothrombin concentration in the blood of a given dose of dicumarol varies from patient to patient and may vary in the same patient from day to day. As hemorrhage following the administration of dicumarol is a definite hazard, the daily dosage of the drug must be controlled by daily and accurate tests of the prothrombin concentration.

Barker *et al*[573a] were among the first to report results of the use of dicumarol in the prevention of venous thrombosis and pulmonary embolism. Their results indicated that an increase in the normal prothrombin time—seventeen to nineteen seconds—to between twenty seven seconds (30 per cent normal) and fifty-eight seconds (10 per cent normal) was effective in preventing postoperative venous thrombosis and pulmonary embolism. They found that significant hemorrhage seldom occurred when the value of prothrombin in the blood was more than 10 per cent. Barker and his associates recommend a dose of 300 milligrams of dicumarol the first day after operation and 200 milligrams the second day. On each subsequent day the prothrombin percentage is determined. If the percentage of prothrombin is more than 20, then 200 milligrams of the drug are given on any day that the prothrombin

is less than 20 per cent, dicumarol is not given. Treatment is continued until the patient is ambulatory, which is usually from seven to fourteen days.

The contraindications to the use of dicumarol listed by Barker *et al.*[3b] are as follows: hepatic insufficiency, renal insufficiency, purpura of any type, blood dyscrasias with a bleeding tendency, particularly thrombocytopenia, subacute bacterial endocarditis, and after recent operations on the brain and spinal cord because of the untoward effects of even a small amount of bleeding. Owing to the risk of bleeding, they advise that extra precautions be taken when dicumarol is administered to patients with open ulcers, granulating wounds, drainage tubes, and operations on the gastro-intestinal tract. Among 1686 postoperative cases treated with dicumarol, major bleeding occurred in 1.9 per cent and two patients died as a result of hemorrhage from the gastrointestinal tract. Barker *et al.* recommend the intravenous injection of 30 to 60 milligrams of synthetic vitamin K (menadione bisulphite) for minor bleeding and a blood transfusion and synthetic vitamin K for major bleeding.

It is generally agreed that venous thrombosis occurs in about 1 per cent of all surgical patients treated by rest in bed after operation and that among the thrombosed cases pulmonary embolism occurs in about 50 per cent and fatal pulmonary embolism in about 20 per cent. After prophylactic dicumarol therapy, Barker and his associates[5, 3b] report that the incidence of thromboembolic episodes was reduced from 43.8 per cent to 1.0 per cent, and the incidence of fatal pulmonary embolism from 18.3 per cent to 0.3 per cent. Among patients with pulmonary embolism, the incidence of thrombotic episodes was reduced from 25.3 per cent to 2.8 per cent, and that of fatal pulmonary embolism was reduced from 5.7 per cent to zero among patients who had venous thrombosis.

In postoperative patients Bauer[5, 4] begins heparin treatment as soon as the earliest signs of venous thrombosis appear in the leg and continues it until the patient is up and about. He combines anticoagulant therapy with remedial exercises in bed and early ambulation after operation. His aim is to prevent pulmonary emboli and the extension of an early thrombosis in the deep veins below the knee and thereby to preclude or lessen the severity of late sequelae of venous thrombosis. He recommends the intravenous injection of 150 milligrams of heparin morning and night, with one or two injections of 100 milligrams during the day. When the patient is ambulatory the dose is decreased to 100 milligrams

night and morning and, finally, to an evening dose of 100 milligrams. In patients with fractures of the lower extremity, heparin treatment in reduced dosage is continued for a couple of weeks. The brand of heparin used contained 80 international units per milligram of water-free substance. Two post-operative patients died of sudden massive pulmonary embolism and the presence of venous thrombosis was not even suspected. Among a group of 438 patients receiving heparin, there were non-fatal pulmonary emboli in 1·3 per cent and a slight bleeding tendency in 2·2 per cent. Bauer considers that there are hardly any contraindications to the use of heparin in venous thrombosis.

Ligation or Interruption of Veins. In 1934, Homans[46] introduced ligation of the superficial femoral vein immediately distal to the profunda femoris for the prevention of pulmonary emboli from thrombosis of the deep veins of the calf. At first the superficial femoral vein was ligated on one side but, as venous thrombosis was commonly found to develop in the calves of both legs (31 per cent), bilateral ligation was recommended. Allen *et al.* have carried out bilateral femoral vein interruptions as a routine prophylactic measure on patients over sixty-five years of age with fracture of the hip, or before operation for cancer or other serious abdominal or pelvic conditions, and for the prevention of thrombo-embolic complications in patients over fifty years of age who present signs and symptoms of venous thrombosis or give a history of pulmonary embolism. The vein interruption was done before, at the time of, or within seventy-two hours after bed rest became necessary. In a series of 458 bilateral prophylactic superficial vein interruptions,[5,6] one patient died of pulmonary embolism and five developed local signs and symptoms of venous thrombosis. There were 26 instances of fatal pulmonary embolism and 55 cases of venous thrombosis in a comparable group of patients not treated by vein interruption. In 110 elderly patients with fracture of the hip treated by vein interruption there were no deaths from pulmonary embolism, but in a comparable control group of patients there were eleven fatal cases of pulmonary embolism. One thousand and sixty patients were treated by vein interruption after venous thrombosis or pulmonary infarction had occurred; less than 5 per cent had further infarcts, but five patients died of recurrent emboli. If pulmonary emboli recur after vein interruption Allen[5,6] recommends anticoagulant therapy. It seems evident that bilateral interruption of the superficial femoral veins is less effective than anticoagulant therapy in the prevention of recurrent pulmonary emboli.

If an acute thrombosis has extended into the femoral vein or higher,

Allen[5 6] recommends phlebotomy and thrombectomy of the superficial femoral vein for the prevention of further pulmonary emboli Others have advocated ligation proximal to the thrombus in the common femoral common iliac, or even inferior vena cava Homans[454] and Allen[6] do not recommend ligation of the common femoral vein on account of the interruption of its muscular branches which may result in congestion and edema Homans found that the collateral venous circulation was more abundant after interruption of the common iliac than the common femoral As the common iliac was often friable and difficult to handle he later[5 7] recommended ligation of the inferior vena cava when bilateral superficial femoral interruption or anticoag ulant therapy failed to prevent recurring pulmonary emboli He sug gests that the operation of vena caval interruption has been somewhat overdone Allen is of the opinion that this major procedure should be reserved for patients having repeated septic infarcts If a propagating thrombus has extended into the common femoral vein or beyond phle botomy and thrombectomy of the superficial femoral vein or ligation of the common femoral or a larger vein proximal to the thrombus may be a safe procedure in the hands of those experienced in vascular surgery but it seems safe to conclude that if this operative treatment is carried out by less experienced surgeons the hazard of the operation and its results may well be even greater than the hazard the procedure is aimed to prevent

In view of the relatively high incidence of recurrent pulmonary emboli in cardiac patients Carlotti *et al*[5 8] carried out femoral vein ligation in sixty patients the majority of whom had serious heart disease Thirty six had ligation of the superficial femoral and fourteen ligation of the common femoral Non fatal pulmonary embolism occurred in two of the fourteen cases after common femoral ligation and in eleven of the thirty six cases after superficial femoral ligation There were seventeen deaths within one month among the sixty patients (8 , per cent) as compared to 50 7 per cent in a control series treated without ligation As the incidence of subsequent pulmonary embolism was less after interruption of the common femoral (approximately 14 per cent) than after interruption of the superficial femoral (approximately 30 per cent) the authors recommend bilateral interruption of the common femoral distal to the sapheno femoral junction and proximal to the profunda femoris as the operation of choice for the prevention of recurrent emboli in cardiac patients They state that femoral vein interruption in these medical patients has been preferred as a rule to

anticoagulant therapy because of the immediate control of the danger (pulmonary embolism) and because of its greater practicability in clearing the threat of recurrent or chronic leg thromboses once and for all An incidence of 21 6 per cent of subsequent pulmonary emboli in the cardiac patients operated upon would not appear to justify the claim that bilateral interruption of the superficial or common femoral veins clears the threat of recurrent venous thrombosis (and its complication pulmonary embolism) once and for all Bilateral interruption of the superficial femoral vein but not of the femoral vein may be a safer and more practicable method of treatment than prolonged anticoagulant therapy but the latter is more effective than vein interruption in the prevention of recurrent pulmonary emboli However, the value of either form of therapy for the prevention of pulmonary embolism in patients with serious cardiac disease is open to question In these patients heart disease and not pulmonary embolism is the primary cause of death, pulmonary embolism which is usually recurrent, may be an immediate cause of death but more often is a contributing cause Fifty per cent of cardiac patients confined to bed for more than a brief period may be expected to have a slowly progressive venous thrombosis of the lower extremities, and 50 per cent of the thrombosed cases have recurrent small pulmonary emboli When rest in bed becomes necessary in the treatment of the cardiac patient, he should wear an elastic stocking and have daily repeated exercise of the legs and feet for the prevention of venous thrombosis and pulmonary embolism The prolonged anticoagulant therapy necessary for the prevention of recurrent pulmonary emboli in patients with serious heart disease is not without risks and is not recommended

There is no general agreement on the relative effectiveness of the three methods of treatment outlined for the prevention of venous thrombosis and its complications or on the indications for their use It is evident from experimental and clinical observations that the routine use of antcoagulants would be the most effective method However the administration of anticoagulants now available is not without risk even in experienced hands and their use may be contraindicated in certain conditions Until an anticoagulant cheaper than heparin and more easily administered or one in which a safe and effective dosage is more easily controlled than dicumarol is made available the use of anticoagulants is not a practical method for routine prophylactic treatment The interruption of veins is also not a practical routine treatment Further, this method of treatment is not effective in prevention of venous throm

bosis with its late sequelae, and is limited in the prevention of pulmonary emboli to emboli having their origin in the ligated veins The increasing tendency toward bilateral ligation of veins proximal to the superficial femoral is further evidence of the limitation of this method of prophylactic treatment Remedial exercises in bed and the wearing of elastic stockings and ambulation as early as possible are practical methods for routine prophylactic treatment of venous thrombosis that can be applied to all medical surgical and obstetrical patients at home or in hospital Hunter *et al*[4, 5] have presented evidence to prove the favorable effect of this treatment on the incidence of venous thrombosis in older patients confined to bed for different disorders It is a method of treatment that should be carried out more systematically on all patients prone to develop venous thrombosis One may agree with Jorpes[4] and others that these measures do not provide full security against pulmonary embolism in surgical patients and that anticoagulant therapy is indicated but maximum security from anticoagulants, which is not full security could be obtained only by routine treatment The incidence of non fatal and fatal pulmonary embolism does not warrant the routine use of anticoagulants

In the selection of surgical patients for anticoagulant therapy Bauer[5, 4] depends on the early diagnosis of local signs and symptoms of acute venous thrombosis and uses heparin to obtain a rapid anticoagulation effect This method of treatment is effective in preventing the extension of an established acute thrombosis in the deep veins of the leg and further pulmonary embolism but has not proved effective in the prevention of unexpected tragic deaths from massive pulmonary embolism for local signs and symptoms of venous thrombosis that can be recognized clinically are nearly always absent in these cases The chief indication for the prophylactic use of anticoagulants following operation would appear to be conditions in which the expected incidence of acute femoral vein thrombosis and its complication massive pulmonary embolism is relatively high such as fractures or a direct trauma of a lower extremity and pelvic operations on patients with carcinoma If laboratory facilities are available for the proper control of dosage dicumarol on account of its cheapness and ease of administration is the anticoagulant of choice for prophylactic use during the first or second day after operation The prophylactic use of anticoagulants following operation is also advocated in patients giving a previous history of pulmonary embolism If the embolism occurred only following a previous surgical operation prophylactic anticoagulant therapy is indicated for a new venous thrombosis

and a fatal pulmonary embolism may develop following the second operation However non fatal pulmonary emboli, often recurrent occur most commonly in older patients confined to bed and more frequently in patients with heart disease or cancer In patients of this group massive pulmonary embolism rarely, if ever, occurs, and anticoagulant therapy may be deferred until signs and symptoms of pulmonary infarction develop following an operation Prophylactic anticoagulant therapy should be combined with remedial exercises in bed and early ambulation

Treatment The treatment of spontaneous or quiet venous thrombosis of the lower extremities may be considered under three headings (1) the treatment of venous thrombosis, (2) the treatment of pulmonary embolism (3) the treatment of postthrombotic sequelae

Venous thrombosis may be an acute process following a major surgical operation fracture or direct trauma of the leg, or childbirth or it may occasionally occur in ambulatory patients Apart from patients with swelling of the limb (phlegmasia alba dolens), no active treatment of the acute thrombotic process is required It is generally believed that the site of origin of the thrombus is in the deep veins of the calf or the plantar veins in the foot Treatment should be directed toward the prevention of the formation of a thrombus or the extension of an established acute thrombus from the deep veins below the knee into the popliteal femoral, or more proximal large veins by methods outlined under 'prevention which are also effective in relieving any swelling that may be present In patients with acute femoro iliac thrombosis (phlegmasia alba dolens) the common practice until recent years has been to keep the swollen limb immobile for a prolonged period to lessen the danger of pulmonary embolism Should an embolus break off from this site it will be a small non fatal pulmonary embolism As pointed out by Homans[504] the proximal end of the thrombus in phlegmasia alba dolens is within the pelvis and is little influenced by movement of the affected limb The patient should rest in a supine or nearly supine position in bed with the leg elevated and wrapped in wool and be encouraged to flex the foot from time to time As increased vasoconstriction is present, reflex vasodilatation by warming the body in a heat cradle or the immersion of an upper extremity in water at 43° C is indicated If pain at the onset has been severe, the edema rapid in development, pulsations of the femoral artery diminished or absent, and if prompt treatment by reflex vasodilation proves ineffective, a paravertebral sympathetic procaine block, as recommended by Ochsner

and DeBakey,[40] should be carried out As an acute femoral thrombosis without visible edema may develop in the opposite limb and be the source of a massive pulmonary embolism it is important that remedial *exercises of the normal limb be not interrupted with the development* of swelling of the other leg The fever and edema will usually subside in one or two weeks Bauer[5 4] recommends heparin treatment of phlegmasia alba dolens combined with active movement of the limbs in bed At present there is no proof that the administration of heparin will result in a more rapid disappearance of fever and edema than by the treatment outlined and the low incidence of fatal pulmonary embolism after childbirth does not warrant its routine use Varying degrees of swelling of the leg in the standing position is an almost constant after-effect of femoral thrombosis with edema Before a patient is allowed out of bed the leg should be fitted with a knee length elastic stocking which should be worn constantly during the day for the first couple of months The patient should be cautioned against the danger of prolonged standing and advised to elevate the leg while resting Later, the patient may go about for short periods without the stocking but it should be worn if swelling develops or the patient expects to be in an upright position for a few hours

Pulmonary embolism causing the sudden onset of extreme shortness of breath pain cyanosis tachycardia and often shock demands prompt treatment Treatment consists in the administration of oxygen in high concentration preferably in a tent the injection of morphine sulphate (one quarter grain) and atropine sulphate (one sixtieth grain), and heparin Murray and Bauer both report striking improvement in shortness of breath cyanosis and tachycardia following the administration of heparin Bauer[4] recommends the intravenous injection of 150 milligrams of heparin every four hours for the treatment of massive pulmonary embolism Owing to its slow action dicumarol is valueless in the immediate treatment of this condition If the patient recovers from the acute attack and if there are no contraindications to the use of anticoagulants therapy by heparin or dicumarol should be continued for the prevention of subsequent emboli or the extension of the acute thrombotic process until the patient is up and about Smaller emboli recurring within a few hours or in a day or two may be fatal in patients with serious heart disease and require the same prompt treatment

A slowly progressive type of venous thrombosis is present in one third to one half of middle-aged or elderly patients confined to bed for more than a brief period The thrombi tend to be short and more

than one may be present in the large veins of the lower extremity, such as one in the posterior tibial or sural and one in the femoral Small recurrent pulmonary emboli, non fatal in the absence of serious heart disease, are present in 50 per cent of cases About 15 per cent of these patients may have a persistent edema of varying degree in the extremity In the other 85 per cent the thrombi would not appear to cause any significant early or late local signs and symptoms of venous thrombosis[4 6]

The treatment of the late sequelae of acute thrombosis of the deep veins of the leg—edema, induration, and ulceration of the lower leg (the post-thrombotic syndrome)—will depend on the severity and duration of the chronic venous insufficiency present Modern methods of prevention of postoperative and postpartum acute venous thrombosis should lower the incidence and severity of these late sequelae

In the early stages of persistent edema and beginning induration of the lower leg, the patient should rest in bed for a few days with the leg elevated, and dorsal and plantar flexion of the foot should be carried out at intervals during the day When the edema subsides and the patient is up and moving about, he should wear an elastic stocking during the day and elevate the extremities while resting He should be advised to keep the skin clean and avoid trauma of the leg and foot If bursting pain in the calf or ulceration of the lower leg is present, the condition probably has followed an acute femoral vein thrombosis, the valves of the vein have been destroyed, and the thrombus has become recanalized Homans[464] has advocated ligation of the superficial femoral, and Bauer,[509] ligation of the popliteal vein to relieve the pain and lessen the increased venous pressure on standing and walking

Postthrombic ulcers are usually infected Infection should be controlled first by rest in bed and the application of warm compresses of Dakin s solution The ambulatory treatment of the ulcer by the application of a foam rubber pad[449] or elastic compression bandage[508] should then be given a trial If the ulcer is of long standing, with marked induration of the skin and fibrosis of the floor of the ulcer, Homans[464] was among the first to recommend the excision of the ulcer and its floor the ligation of any feeding veins, and the covering of the denuded area by a split thickness skin graft Recently, Linton[508] has called attention to the frequency of recurrence of postthrombotic ulceration in patients subjected to different methods of treatment He recommends the removal of any dilated superficial veins and communicating veins on the inner side of the leg the ligature and division of the superficial

femoral vein and the wearing of an elastic stocking when the patient is ambulatory For details of the treatment the reader is referred to the original article In older patients with signs and symptoms of an associated chronic obliterative arterial disease, lumbar sympathectomy should be considered for the improvement of the cutaneous circulation and the nutrition of the skin

The treatment of phlegmasia cerulea dolens consists in the relief of increased vasoconstriction by warming the body in a heat cradle or immersing an unaffected extremity in water at 43° C or by a paravertebral block of the sympathetic ganglia by procaine and the administration of heparin followed later by dicumarol to prevent the extension of the venous thrombosis If gangrene is present its treatment will depend on its extent and the degree of toxemia

Primary Axillary Vein Thrombosis of Effort Thrombosis of any form in the veins of the upper extremity is uncommon Occasionally in young healthy men muscular effort with the arms abducted or extended is followed by pain in the shoulder or arm The arm becomes cyanosed and edema may develop immediately or in the course of a few hours or days No systemic reaction follows Palpation of the axilla usually reveals a tender cord corresponding to the axillary vein Later the superficial veins in the region of the affected shoulder and the upper chest become dilated indicating a chronic venous obstruction

The mechanism of this disturbance is obscure Most observers are agreed that trauma the result of muscular effort is the inciting factor in the production of this clinical syndrome referred to as primary axillary vein thrombosis of effort Compression of the axillary vein or injury to its wall by the costocoracoid ligament and the subclavius muscle during muscular effort with the arm in an abducted position would appear to be responsible for the disturbances that subsequently develop[530, 531] Gould and Patey[531] are of the opinion that a sudden contraction of the subclavius muscle causes a rupture of the subclavio axillary valve which is followed by thrombosis of the vein Infection is not a factor

According to Matas[53] mild cases may recover in six to eight weeks but in more severe cases the disability may last for months or even years and relapses may occur unless the patient avoids strenuous exercise of the affected arm The immediate treatment consists in rest in bed with the arm elevated in a heated cradle If the edema does not disappear in a couple of days an elastic bandage should be applied from the wrist to the shoulder and the patient be allowed to get up he should not

resume work with the arm for a period of two months Anticoagulant therapy or ligation of the veins and thrombectomy are not indicated

Phlebitis There are two main types of phlebitis (1) non infective—simple or aseptic phlebitis, (2) infective phlebitis—non suppurative and suppurative

Non infective Phlebitis Severe physical or chemical injury to the wall of a vein causes an inflammatory reaction which usually results in thrombosis secondary to the phlebitis The common causes are injury to a vein by a blow, repeated venipuncture, or the injection of sclerosing solutions Following the organization of an acute venous thrombosis a secondary noninfective phlebitis of varying degree occurs

Infective Phlebitis A non-suppurative phlebitis with thrombosis may develop early in the course of infectious diseases and should be differentiated from a spontaneous thrombosis developing late in an infection such as typhoid fever or pneumonia Micro-organisms are absent from the lesions No special treatment apart from rest in bed until the local inflammatory reaction has subsided is required

Suppurative phlebitis is a more severe and dangerous form of infective phlebitis The causative micro organism, usually staphylococcus may spread from an adjacent abscess or local cellulitis and attack the wall of a small or large vein and a thrombus rapidly forms If the thrombus is infected it may soften and infected emboli spread to distant organs of the body resulting in the formation of small abscesses—pyemia In some cases the center of the thrombus liquefies from the action of leucocytes and organisms and a collection of pus is formed within the lumen of the vein

The signs and symptoms of suppurative phlebitis with secondary thrombosis depend on the site the size and extent of the vein involved the nature of the infection, and the presence or absence of septic emboli In the superficial veins of the extremity, a suppurative phlebitis usually follows a local cellulitis The affected vein is firm and painful the overlying skin reddened, and a moderate edema and lymphangitis are present The development of recurrent chills, sweating, tachycardia respiratory symptoms, fever and leucocytosis mark the onset of septicemia and pyemia Prompt treatment of the primary focal lesion and the adminstration of adequate dosage of penicillin or other antibiotics depending on the sensitivity of the infecting organism, is important

Thrombophlebitis Migrans (Recurrent Idiopathic Thrombophlebitis) Thrombophlebitis migrans is a primary disease of unknown origin, char

acterized by a migrating and recurrent thrombophlebitis affecting segments of veins, usually peripheral superficial veins, less often small veins of lungs and abdomen, and rarely, heart and brain In 1866 Paget[533] called attention to a recurrent and migrating thrombophlebitis of the superficial veins occurring in patients with gout or giving a family history of gout Briggs [534] in 1905, described a recurrent thrombophlebitis of the superficial veins of unknown origin under the term idiopathic recurrent thrombophlebitis Harkavy [535] remarked upon the segmental involvement of the veins of the upper and lower extremities Under the title thrombophlebitis migrans Moorhead and Abrahamson [536] and, later Ryle[537] described the clinical manifestations and course of the disease and called attention to the involvement of veins of the lungs mesentery heart, and brain Similar cases have since been described by others[538, 539, 540, 541] In a fatal case of thrombophlebitis migrans of the superficial veins complicated by bronchogenic carcinoma reported by Warner and Dauphinee[541] the patient developed a paroxysmal tachycardia A clinical diagnosis of thrombophlebitis migrans with involvement of a coronary vein was made and later confirmed at the postmortem examination

The disease begins as an acute phlebitis involving a short segment of one of the superficial veins of the leg or arm A mild fever is present The acute manifestations subside in a week or two but a segment of the same vein or other veins tends to become involved at irregular intervals The disease tends to run a protracted course but the ultimate prognosis is favorable fatal cases being uncommon Involvement of visceral veins usually is preceded by lesions of one or more superficial veins and—depending upon the site of the lesion—lung abdomen, heart or brain cause symptoms simulating non fatal pulmonary embolism mesenteric infraction mild cardiac infarction or cerebral vein thrombosis The prognosis in visceral thrombophlebitis usually is favorable

The cause of the disease is unknown The onset of a thrombophlebitis after an upper respiratory tract infection or an abscessed tooth suggests infection as a possible cause but blood cultures[536, 541] and cultures of thrombosed veins excised during life[540, 541] have given negative results The disease occurs in both the young and middle aged and is more common in men than women In early acute lesions the lumen of the vein has been found to contain a recent laminated red clot with necrosis of the intima and part of the media but no inflammatory reaction in the adventitia[541] At a later stage acute lesions have shown organization of

the thrombus with infiltration of the wall with connective tissue cells[540] The inflammatory nature of the lesion and its segmental distribution simulate the lesion present in thromboangiitis obliterans, but arteries are not involved Apart from the removal of definite foci of infection after acute manifestations have subsided, treatment of the disease has been expectant and symptomatic Hormonal therapy is ineffective Vinther Paulsen[542] reports no recurrence of thrombophlebitis in two cases following prolonged treatment by dicumarol

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CHAPTER XIV-A

DISEASES OF THE AORTA

By ROY W SCOTT

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ACUTE AORTITIS

Acute inflammation of the aortic wall is a rare disease and is usually associated with mitral or aortic endocarditis A few cases however, of primary acute aortitis with positive blood cultures are on record in which no mural or valvular endocarditis was present There are two possible routes by which a blood borne infection may spread to the aortic wall through the vasa vasorum or by direct implantation The latter route appears the more likely since the histological changes of acute suppuration are usually confined to the intima

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Functional Disturbances

It is frequently difficult to estimate the functional significance of arteriosclerotic changes in the aorta as associated similar changes in other large vessels commonly influence the clinical picture However there are certain functional disturbances definitely attributable to intimal disease of the aorta which concern us here Occasionally advanced arteriosclerotic changes at the root of the aorta involve the sinuses of Valsalva and the cusps of the aortic valve In the absence of chronic endocarditis the leaflets are seldom much reduced in size but thickened and rigid and in some cases almost completely calcined More or less immobile they project into the lumen of the aorta and appreciably narrow the orifice The left ventricle is hypertrophied the well known signs of aortic stenosis appear and the clinical picture toward the end may be that of heart failure Frequently to be sure there is an associated chronic endocarditis complicating the picture yet examples of aortic stenosis due to arteriosclerotic changes of the aortic orifice are seen

The contents of atheromatous ulcers or bits of thrombi from the site of such ulcers may be set free in the aortic stream Circulating as emboli they may occlude vessels in any part of the greater circulation and thus cause a variety of functional disturbances On the other hand such vascular accidents may pass unnoticed particularly in the viscera as the kidneys or spleen and be evidenced at autopsy by healed infarcts

Besides serving as a conduit for the passage of blood from the heart the aorta is endowed with two attributes elasticity and resilience important factors in the maintenance of the circulation By virtue of its elasticity the normal aorta absorbs the shock of ventricular systole so that there is little or no visible systolic excursion of the peripheral arteries However as the aorta approaches the state of a rigid tube from arteriosclerotic changes in the wall more and more of the force of ventricular systole is transmitted peripherally clinical evidence of which is afforded by the augmented excursion of such palpable arteries as the carotids brachials and femorals Indeed the abrupt and forcible anacrotus of the peripheral pulses is an important diagnostic sign of an inelastic aorta

As the arteriosclerotic aorta is impaired in what we may call its systolic function it fails and to a corresponding degree in its diastolic function that of maintaining the diastolic blood pressure Here again the peripheral arteries take over this function and we find clinically not only the forcible systolic thrust mentioned above but also an augmented diastolic recoil an adjustment to compensate for the deficiency of the aorta This increased work on the part of the peripheral arteries may be a factor in the development of peripheral arteriosclerosis

and inner portions of the media, regions supplied not by the vasa vasorum but by the circulating blood The writer has seen one instance of acute aortitis complicating syphilitic aortitis Since there are no characteristic clinical signs of acute aortitis, the condition must be regarded as an accidental autopsy finding

Arteriosclerosis of the Aorta

Anatomical Changes

The most common affection of the aorta is arteriosclerosis Indeed, one rarely sees at autopsy an adult aorta free of arteriosclerotic changes These usually appear first as slightly elevated, yellow streaks on the posterior wall about the openings of the intercostal arteries Microscopic sections through these areas show a thickening of the intima from newly formed connective tissue through which is scattered a varying amount of fat As the process advances the intima becomes roughened by irregularly shaped, pearly or transparent plaques which give to the arteriosclerotic aorta its most characteristic appearance

A section through these elevated areas of intimal thickening shows irregular deposits of fatty material covered by dense connective tissue In a more advanced stage hyalinization or necrosis of the plaques occurs producing the so called atheromatous ulcer In the cavity or at the edges of such ulcerated areas thrombosis frequently occurs There is also an irregular deposition of calcium salts, which may form thin stony scales over the surface of the aorta, or in some instances the vessel may be converted into a calcified tube Even in advanced cases the arteriosclerotic changes are confined largely to the intima, indeed this may show extensive disease with little alteration in the underlying media

The distribution of the arteriosclerotic process in the aorta, as in other vessels, varies widely In some instances the disease affects the whole vessel, in others it is fairly well localized There is, for example, an interesting but hitherto unexplained association between extreme old age and arteriosclerotic involvement of the root of the aorta that is the first 3 to 4 centimeters of the vessel My attention first was called to this fact by Prof J Erdheim of Vienna He observed that in individuals who have reached the age of 80 or 90 years, the first 3 or 4 centimeters of the aorta are singularly spared of any arteriosclerotic involvement even if the rest of the vessel shows advanced changes Indeed the autopsy findings are so consistent regarding this point as to justify the statement that individuals having marked arteriosclerotic changes of the first few centimeters of the aorta do not survive beyond about 70 years

accumulate about the middle of the 19th century With the general acceptance of the work of Dohle in 1903 and the demonstration by Kuter in 1906 of treponema pallidum in sections of syphilitic aortas the major problems concerning the rôle of syphilis in diseases of the aorta may be regarded as settled

Anatomical Changes

The gross appearance of an aorta, the seat of syphilitic aortitis, varies to some extent with the age of the patient In people beyond the fourth or fifth decades of life the simple intimal changes due to arteriosclerosis may overshadow completely those of syphilis and histological study may be necessary to establish the diagnosis In typical cases one finds the characteristic wrinkling and puckering of the intima and a varying number of depressed scars all of which give the lining of the vessel a roughened appearance These changes may be seen throughout the entire length more commonly however the root and the ascending arch show the more marked involvement In rare instances the lesion is confined to the abdominal aorta Frequently the process is sharply localized at the root of the vessel where it may distort the aortic valves or occlude the mouths of the coronary arteries The ultimate destruction of the media undermines the aortic wall leading to localized or diffuse dilatation

The first evidence of syphilis may be a widening of one or all three commissures of the aortic leaflets This is an important point for the macroscopic diagnosis of early lesions The commissural involvement also may be the only gross evidence of syphilis in old cases in which the aorta shows marked simple arteriosclerotic changes

Microscopic changes produced by syphilitic disease of the aorta like the gross changes vary somewhat with the age of the lesion and the severity of the process In early cases the most consistent findings are endarteritis obliterans of the vasa vasorum and perivascular infiltration with lymphocytes in the adventitia At this stage the media may show myxomatous degeneration and some areas of necrosis independent of the lymphocytic infiltration findings which suggest that the early changes in the media are due to nutritional disturbances In older cases one finds patches of extensive necrosis in the media which may become organized as shown by new formation of vessels endothelial cells and young connective tissue The perivascular infiltration of the newly formed vessels suggests that the process does not heal but proceeds as a chronic inflammation Associated with the scarring so commonly seen in the media there is interruption of the elastic lamina and a consequent weakening of the aortic wall On this basis is to be explained the development of aneurysms

Past writers on the subject were concerned with late cases in which the most striking histological changes occurred in the media and for this reason

Arteriosclerosis of the aorta and larger vessels may cause no functional disturbances and is a lesion by no means incompatible with a ripe old age In some instances the blood pressure is not altered, in a large group, however, there is little or no elevation in the diastolic pressure but a moderate elevation in the systolic pressure, the so called systolic hypertension Generally speaking, such patients have a different clinical course and a better prognosis from those individuals in whom the vascular changes are confined to the smaller arteries and arterioles

Etiology

The etiology of arteriosclerosis is not known In spite of a great amount of work on the subject in the past century, we have little more exact information concerning the pathogenesis of arteriosclerosis than did Lobstein who in 1831, introduced the term to denote a ' hardening and thickening of the arteries The tissue changes in arteriosclerosis appear insidiously and develop slowly over a long period of time during which many noxious agents may act singly or in combination to influence the development of the process Since fundamental knowledge concerning the cause of arteriosclerosis is lacking, we have a wide variety of ideas advanced to explain the condition These are in many instances as MacCallum says, ' so vague and ill supported that it is wearisome to discuss them Conceptions easy to formulate may be difficult to prove and such is the case regarding the etiology of arteriosclerosis Some of the more frequently mentioned factors are age, hard muscular work, high blood pressure, and hereditary tendencies but a critical survey of past writings on the subject shows no indisputable evidence that any of these has a direct bearing on the etiology On the other hand, experiments designed to produce the lesion of human arteriosclerosis in animals suggest, but do not prove that infections intoxications and abnormal diets may be important etiological factors Thus far the experiments dealing with the effect of unbalanced diet and with mechanical disturbances such as heightened blood pressure appear to have produced most closely some of the lesions of arteriosclerosis as observed in man

Syphilitic Aortitis

Fortunately in the consideration of this subject no such obscurity surrounds the etiology, as we found in the case of simple arteriosclerosis That syphilis affected the aorta leading to atheroma was suggested by Ambrose Pare in the 16th century, and Morgagni in 1761 attached much importance to syphilis as a cause of aneurysm Definite proof that syphilis involved the aorta began to

The percentage of positive reactions reported by past authors varies considerably in the writer's series it was 85 per cent

In somewhat more advanced cases than we have thus far considered cases in which the disease has produced gross anatomical alterations in the aortic will we have certain objective signs to aid in diagnosis These depend on the fact that the syphilitic aorta is less elastic than normal Under physiological conditions most of the kinetic energy generated by the systole of the left ventricle is stored as potential energy by the expanding aortic wall In other words the shock of systole is absorbed As the aorta loses its elasticity more of the force of ventricular systole is transmitted peripherally and as we saw above in the case of simple arteriosclerosis there is a wider systolic excursion of the arteries springing from the arch Thus a forcible systolic thrust over the carotid arteries unaccompanied by a diastolic collapse as seen in insufficiency of the aortic orifice indicates an inelastic aorta This same overactivity may occur in parts of the aorta itself particularly in the transverse arch under which circumstances one palpates over the manubrium sterni a systolic impulse and diastolic impact This phenomenon is more conspicuous if the aorta is dilated because the excursion of the wall is then more accessible to palpation in the intercostal spaces near the edge of the sternum

Syphilis frequently causes an elongation of the aorta with an upward displacement of the arch The activity of the vessel then may be felt by deep pressure in the supra sternal notch Also in some instances of elongation the heart is displaced downward and outward so that the maximum apical thrust may be felt in the sixth intercostal space beyond the mid clavicular line Even before the development of frank aneurysm one occasionally finds disparity of the radial or carotid pulses on the two sides due to narrowing of the mouths of one or more of the arteries originating from the aortic arch In certain instances the process in the aorta may be sharply localized at the root so that the first and only sign of the disease may be an alteration in the sounds originating at the valve area or the presence of physical signs indicative of free aortic regurgitation

Valuable objective evidence to substantiate the diagnosis of syphilitic aortitis is afforded by x ray The most important x ray finding in early cases is an increase in the diameter of the aorta We have several methods for measuring the width of the aorta but unfortunately none of them is entirely satisfactory Perhaps the best all round method is the fluoroscopic. In the hands of the experienced an opinion as to the presence or absence of dilatation can be relied upon even though it lacks numerical exactness In evaluating x ray appearance of the aorta due consideration must be given to the size and shape of the thorax position of the diaphragm position of the heart the presence of isthmus stenosis or hypertension factors which may so alter the aortic

the term "mesaortitis syphilitica" was applied However, "aortitis syphilitica" seems more appropriate because, as the study of early lesions shows the medial involvement appears to be secondary and of the nature of nutritional disturbances, the result of progressive occlusion of the vasa vasorum

Diagnosis of Syphilitic Aortitis

As in the case of many chronic diseases, success in the therapy of syphilitic aortitis depends on early diagnosis This is frequently difficult and in many instances impossible How often we are surprised to see at post mortem indisputable examples of syphilitic aortitis that were clinically silent! Certain it is that many patients never consult the physician until the disease has produced structural defects in the aorta or at the aortic orifice

In discussing the diagnosis, many writers stress the importance of certain subjective sensations such as substernal pain, oppression, anginal attacks, and paroxysmal attacks of dyspnea Such symptoms may afford the one clue to diagnosis in some cases, but many exceptions are seen, especially among the working class commonly observed in a charity hospital Particular attention was paid to this point by the writer in a series of 150 hospital cases which later came to autopsy Symptoms other than those from aneurysm or myocardial failure were seldom noted It appears therefore that the presence of a syphilitic inflammation in the aorta is not the sole factor concerned in the production of symptoms any more than coronary sclerosis is the sole cause of angina pectoris In both instances the nervous organization of the individual, the receptivity of the nervous system to afferent visceral impulses, probably plays an important role in determining the symptomatology in a given case If then we are to recognize syphilitic aortitis before it has changed the gross architecture of the vessel the diagnosis must be largely inferential, particularly in patients who have no symptoms Here it is important that the physician keep in mind certain well established facts first that latent syphilis more frequently involves the aorta than any other viscus second, that syphilis may be present as a chronic inflammation in the aorta for more than forty years and the patient present no signs or symptoms of the disease For example, in a series of 34 males who died of syphilitic aortic insufficiency the shortest interval between the primary infection and death was five years, the longest 44 years with an average of 20 years The fact that an individual is the parent of normal children is not a sufficient criterion for the exclusion of the existence of aortic syphilis One frequently sees clear examples of syphilitic aortitis, particularly in males who were the fathers of healthy families

The significance of a positive Wassermann reaction in the early diagnosis of syphilitic aortitis is apparent since it may be the only positive evidence of syphilis

mine one may use the trivalent organic arsenical mepharsen which is simpler to prepare and has is somewhat less toxic than neoarsphenamine The dose of mepharsen is 0 01 gram increased gradually to a maximum of 0 06 gram

In well compensated patients with aortic insufficiency who have never had a cardiac breakdown the above course of treatment may be instituted If anginal symptoms due to narrowed or occluded coronary ostia dominate the clinical picture bismuth and potassium iodide are used but most clinicians advise against the use of arsenicals in such cases and malarial therapy or any other type of shock treatment is absolutely contraindicated

Syphilis of the Aortic Valve Area

We have seen above that syphilis of the aortic wall may lead to certain structural alterations i e loss of elasticity elongation of the vessel and diffuse or localized dilatations Such changes naturally impair to a greater or lesser degree the function of the aorta and may in the case of aneurysm cause a variety of disturbances from compression of contiguous structures Added significance however is attached to syphilis of the valve area because in this situation the disease becomes an important cause of heart failure So long as the valve area is spared marked alterations may occur in the aortic wall and yet the heart is not embarrassed For example one frequently sees diffuse dilatations or large aneurysms of the aorta in individuals who show clinically no evidence of heart disease On the other hand the ravages of syphilis may be localized at the root of the aorta leading to in ufficiency of the valve or to narrowing of the coronary mouths while the remainder of the vessel is little altered In such instances the clinical picture is one of heart failure from beginning to end We may separate therefore patients with syphilitic aortitis into two groups one with and one without the clinical signs and symptoms of cardiac failure An equally sharp line also may be drawn from the autopsy findings in the two groups those cases with no clinical evidence of myocardial failure have little or no distortion in the architecture at the root of the aorta and the heart is normal in size while those patients with heart failure during life have at post mortem an enlarged heart and a diseased aortic orifice

Syphilitic Occlusion of the Coronary Arteries

Syphilis at the root of the aorta frequently involves the mouths of the coronary arteries leading to constriction of the orifices One out of four cases in the writer s series had some narrowing of the coronary orifices while two had total obliteration of the mouths of both vessels That such hearts are able to carry on as long as they do illustrates a remarkable adaptation to impairment

silhouette as to make it simulate dilatation of syphilitic aortitis A dilated aorta in a middle aged individual in the absence of the above factors is almost surely syphilitic in origin The dilatation in early cases, while it may involve the entire aorta usually is localized The place of predilection is in the ascending aorta By x ray this dilatation appears as a spindle shaped enlargement best seen in the second oblique position It will be noticed in such cases that local density is increased and pulsations are more marked In older cases, even though dilatation may be general it may not be equal throughout

Upon dilatation depends the second sign, namely an increase in density This increased density is usually attributed to the increase in the cross diameter of the column of blood However, cases are seen in which the diameter of the vessel is only slightly increased or is normal and yet the density is quite marked In such instances this density is due mainly to the thickness of the vessel wall

The increase in the length of the aorta is a significant finding Normally the highest point of the transverse arch is 2 to 3 cm below the level of the sternoclavicular joint This space in early cases of syphilitic aortitis may be partially obliterated In well marked cases the arch is seen to reach beyond the jugular notch into the root of the neck

Treatment of Syphilitic Aortitis

It is in the early stage of syphilitic aortitis that we may expect definite results from treatment Any medication that tends to allay the process in the aorta and thus prevent its spread to the aortic orifice or retard the development of aneurysm may add years to the patient s life The course of treatment will depend to a large extent on the age and physical condition of the patient Cardiac or renal disease active tuberculosis malnutrition anemia etc should be recognized and evaluated in any proposed scheme of specific therapy With sound kidneys and no evidence of cardiac involvement such as aortic insufficiency coronary ostia narrowing and provided a saccular aneurysm is not present one is justified in using a fairly intensive course of treatment

Ten to twelve weekly injections of bismuth salicylate 0 2 gram with potassium iodide 30 to 50 drops of a saturated solution three times daily, are given for one week then five drops three times a day may be administered over a period of several months The bismuth and iodide course then is followed by a course of neoarsphenamine beginning with a 0 1 gram dose and increasing by 0 05 gram weekly to a maximum of 0 6 gram Ten to twelve neoarsphenamine injections constitute a course A continuous method of treatment alternating bismuth and iodides with neoarsphenamine should extend over a two year period and thereafter the patient should receive an annual course of bismuth and iodides alternating with neoarsphenamine As a substitute for neoarsphena

It will be recalled that normally, adjacent aortic leaflets have a common site of attachment to the aortic intima called the commissure and to refresh



FIG 1 — Showing the first part of the aorta and the aortic val e in a case of syphilitic aortitis in which the mouth of the left coronary artery is completely occlu led at the point indi cated by the arrow [illegible]

one s memory of the normal architecture it is only necessary to inspect the pulmonary orifice in a given case In syphilis the region of the commissure is thickened and is usually the seat of a hyaline plaque while the site of

of their natural blood supply, time being the important factor in it. The orifices of the coronary arteries are slowly occluded by the syphilitic process in the aorta so that ample time is afforded for the development of compensatory mechanisms. If one vessel is occluded collateral circulation with the other may be established. An even more important compensation however, is afforded by the Thebesian system of vessels. The true significance of these vessels was demonstrated by Wearn, who in an ingenious set of experiments demonstrated direct communication between the coronary arteries and the chambers of the heart through the Thebesian vessels. Using similar methods he showed that communications exist between the larger coronary veins and the Thebesian vessels. As Wearn mentions the best evidence that the Thebesian vessels actually can take over the function of the coronary arteries is supplied by observations on patients with complete obliteration of both vessels from syphilis. In two such cases observed by the writer there was clear evidence from the history and autopsy findings that the heart maintained an adequate circulation certainly for days and in all probability for weeks without any blood supply through the coronary arteries. As important as the Thebesian circulation may be it can not be regarded as a perfect compensation because hearts entirely deprived of their coronary supply soon fail. In Fig. 1 is shown a syphilitic aortic orifice with complete occlusion of the orifice of the left coronary artery.

Aortic Insufficiency

Anatomical Changes. — We may now consider the most common functional defect at the aortic orifice caused by syphilis, namely, aortic insufficiency. This lesion is more commonly the result of leaflet involvement, although an occasional instance of primary ring dilatation is seen. Here the valve leaflets may be actually larger than normal. When not seriously involved such elongated leaflets may even seal a dilated orifice in diastole. In order to appreciate the anatomical changes that one finds in the leaflets it is necessary to trace the development of the syphilitic process at the aortic orifice, the spread of syphilis from the aorta to the valve area. As is well known the leaflets in late cases show a variety of architectural distortions. All however are of such a nature as to cause functional insufficiency of the orifice and never stenosis. The leaflets are shrunken, thickened and more rigid than normal. They may be reduced in size to mere fibrous bands. The free margin usually is markedly thickened presenting a rolled appearance. The valve attachments at the commissures frequently are displaced so that the leaflets appear to sag as seen in Fig. 2. However the body of the valves may be deformed, the most characteristic lesion of syphilis is found at the commissure.

It will be recalled that normally adjacent aortic leaflets have a common site of attachment to the aortic intima, called the commissure and to refresh



Fig. 1.—Showing the first part of the aorta and the aortic valve in a case of syphilitic aortitis in which the mouth of the left coronary artery is completely occluded at the point indicated by the arrow. (Th[illegible] Todd.)

one's memory of the normal architecture it is only necessary to inspect the pulmonary orifice in a given case. In syphilis the region of the commissure is thickened and is usually the seat of a hyaline plaque while the site of

attachment of neighboring leaflets is separated, giving a gross picture of a widened commissure

This commissural lesion merits particular attention because, in the first place, it is the most constant sign of syphilis of the valves in late cases, and secondly, it is the first lesion to be seen in early cases of valve involvement For example, Fig 3 shows a normal sized heart of a negro male, aged 40, who died of lobar pneumonia Syphilis of the aorta was an accidental autopsy finding Note the widening of the commissures and the normal appearance of



Fig 2 — Showing the sagged appearance of the aortic valves in syphilis

the valve cusps Here is a clear example of early valve involvement a lesion as yet of no functional significance Had this individual not succumbed to pneumonia he might well have developed aortic insufficiency and died of heart failure Another early lesion clinically silent, is shown in Fig 4, the heart of a twenty two year old colored female also dead of lobar pneumonia Note the normal aortic intima, and the widened commissure without deformity of the valves These early lesions may be contrasted with a late one shown in Fig 5, the heart of a forty two year old colored male Here the syphilitic process is

localized at the aortic root Note the widening of all commissures and the thickened retracted leaflets This patient during life had aortic insufficiency and died of cardiac failure



Fig 3 — Shown an early case of syphilis of the aortic valve which was clinically silent Note the characteristic separation of all three commissures marked by arrows and the normal appearance of the valve cusps

A somewhat different deformity of the valve cusps is seen in Fig 6 This shows marked adhesion of the lateral margins of the two leaflets to the adjacent aortic intima with the original site of attachment still visible

The significance of the commissural lesion and the role it plays in the later valve deformity is best understood by a study of the histological changes



FIG 4 — The heart of a 22 year old female showing the early lesion of syphilis of the aortic valve Note the sharply circumscribed lesion involving the commissure

The following account is based on a study of 71 autopsied cases made by the writer in collaboration with Dr Saphir Blocks were taken from various parts



Fig 5 — Shows the advanced lesion of syphilis rather sharply confined to the aortic orifice Note the shrunken valves and the widening of the commissures

of the aorta the commissures and the valve cusps In three cases serial sections of the entire aortic ring were studied Sections from the region of the com

missures in early cases with little valve deformity show the same microscopic changes as described above in early syphilitic aortitis

There is a new formation of small vessels extending from the intima of the aorta through the commissures These show marked proliferation of endothelial

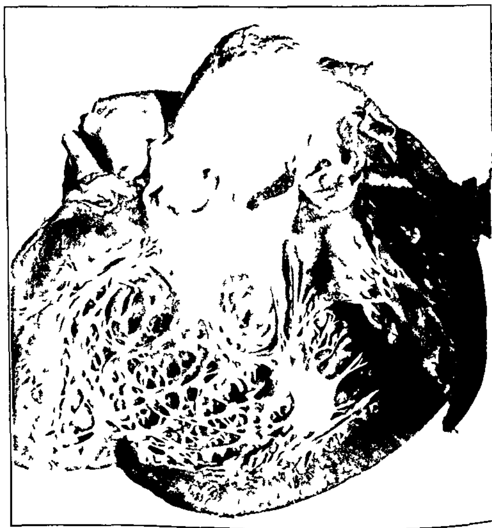


Fig 6 — Showing a less common type of deformity of the valves caused by syphilis. Note the fusion between the lateral valve margins and the adjacent aortic intima

cells leading to partial or complete occlusion of their lumina The portions of the media and the adjacent intima show changes characteristic of mucoid degeneration In older lesions the degenerative changes are less pronounced, while those of chronic inflammation are more conspicuous Serial sections show that h

alinization and chronic inflammatory processes are more marked the closer to the adherent portion of the cusp the sections are taken In the mid portions of the valve leaflets only fibrosis is seen with very few cells and no vessels

From our observations it appears that syphilis spreads from the aorta to the margin of the aortic leaflets through small vessels at the commissure For this reason the earliest lesion is found in the region of the commissure Syphilitic changes in the small vessels obliterative arteritis lead to nutritional disturbances which are followed by chronic inflammatory changes in both the lateral margins of the leaflets and the adjacent aortic intima of the sinus of Valsalva, finally producing adhesions between these two regions which later may become hyalinized This fusion gives the gross picture of a separation

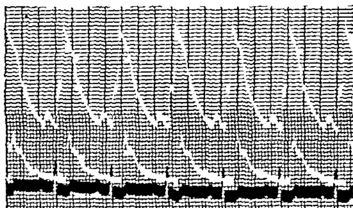


Fig , — The subclavian (upper) and radial (middle) curves optically recorded and lead 2 of the electrocardiogram from a case of syphilitic aortic insufficiency Courtesy of Dr H Feil

of the commissure the earliest and most characteristic lesion of syphilis of the aortic valve

We see therefore that the primary lesion in syphilitic aortic insufficiency is at the root of the aorta a true syphilitic aortitis The valve involvement is secondary and due to extension of the process by way of small vessels at the commissure The frequency of latent syphilis at the root of the aorta as seen at autopsy is probably due to the fact that in this region we find the richest supply of vasa vasorum Since syphilis is a primary disease of small vessels it is therefore of greater significance in areas containing the largest number of vasa vasorum

Dynamics of Aortic Insufficiency — The disturbance in the peripheral circulation from incompetency of the aortic valve may be studied by accurate

registration of the peripheral pulses In the accompanying records are shown the subclavian (upper) and radial (middle) pulses registered optically, Fig 7 from a case of aortic insufficiency due to syphilis, and Fig 8, from a case of rheumatic aortic insufficiency Here (Fig 7) we note that the pulse is large, the anacrotus rises suddenly, almost perpendicularly, the summit is sharp, of brief duration, and the catacrotus falls away steeply to the incisura Thus it is seen that the Corrigan quality is due to (a) the abrupt rise, (b) the sharp, ill sustained summit and (c) the rapid descent of the pulse The radial curve shows in a modified way the changes seen in the central pulse The pulse wave is usually monocrotic and has an abrupt rise and fall The pulse of syphilitic aortic insufficiency differs from that observed in aortic insufficiency of rheumatic origin in that the latter rises less steeply, the summit is not as sharp and is

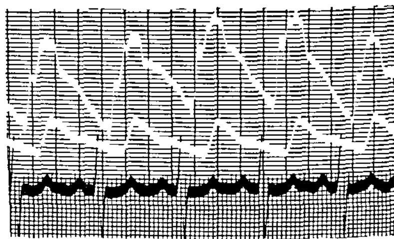


Fig 8 — The subclavian (upper) and radial (middle) curves optically recorded and lead of the electrocardiogram from a case of rheumatic aortic insufficiency Courtesy of Dr H Feil

surmounted by fine vibrations the fall is not so precipitous (See Fig 8) The top of the pulse is usually placed near the end of maximum ejection These changes are observed in the radial pulse in a modified form, the summit is rounded, is sustained for a longer period and is often broken by two waves (bisferiens) The pulse of syphilitic aortic insufficiency (Fig 7) rises abruptly its sharp peak is quickly attained and its descent is rapid The pulse of rheumatic aortic insufficiency (Fig 8) on the other hand has features of aortic stenosis the less steep rise, the rounded summit reached near the end of ejection and cut by fine vibrations while the catacrotus is less precipitous In the pulse of both pathological conditions the ascent is often broken by a small wave or jog nearly half way up Likewise in both pulses the fall is steepest before

the dicrotic notch and the dicrotic wave in the radial is often ill defined or lacking

Diagnosis of Aortic Insufficiency — A clear conception of the pathological changes ultimately leading to functional insufficiency of the aortic orifice is indispensible for clinical diagnosis We have seen that syphilis may continue as a chronic inflammatory process in the wall of the aorta for many years and yet cause no signs or symptoms The root of the vessel and even the com missures of the valves may be involved without insufficiency of the orifice Sooner or later, however the leaflets are deformed or the ring is dilated and aortic insufficiency as a clinical phenomenon appears From the nature of the pathological changes we see that the lesion may be insidious in onset and for this reason it follows that aortic insufficiency appearing out of a clear sky in an adult with a negative cardiac history must be regarded as syphilitic until proved otherwise

It was stated above that it was difficult and sometimes impossible to detect syphilitic aortitis in an early stage Here we may emphasize the fact that the signs of beginning incompetence of the aortic orifice may be the first demon strable evidence of syphilitic aortitis Any abnormality in the auscultatory signs over the aortic orifice must be regarded with care in an early case A faint diastolic or a to-and fro blow may be heard at the second right interspace or over the anatomical site of the aortic orifice at the left sternal border Un fortunately, however the physician seldom sees early cases that is before the appearance of cardiac symptoms On the other hand there may be a natural paucity of incipient cases because as we have seen above the anatomical lesion responsible for the valve defect does not remain stationary but tends to progress In other words an early leak soon becomes a free regurgitation At this stage of the disease provided the heart is well compensated we find the well known peripheral vascular signs of aortic insufficiency There is a localized and more or less forcible systolic thrust over the apex of the left ventricle which may be displaced downward and outward in the sixth inter space beyond the mid-clavicular line In the third and fourth left intercostal spaces over the manubrium, and in the aortic area one most frequently hears a to-and fro murmur The systolic element at times is louder than the diastolic and a systolic thrill may be palpated over the base of the heart Such findings naturally suggest a narrowing of the aortic orifice but if syphilis is the cause no actual stenosis is found at autopsy Thickened and rigid aortic leaflets unlike the delicate normal cusps do not approximate the aortic wall during systolic ejection but project into the blood stream and afford sufficient obstruction to produce a murmur and in some cases even a thrill But the syphilitic aortic orifice no matter how suggestive the clinical signs of stenosis may be is wider than normal Stenosis in the sense of an actual

impediment to the flow of blood from the left ventricle to the aorta is not caused by syphilis

Auscultation sometimes reveals a snappy or a tympanitic valve closure sound followed immediately by a regurgitant murmur This is a valuable diagnostic sign of dilatation of the aortic ring Fairly normal leaflets are approximated during diastole, producing the closure sound, but being unable to seal the dilated orifice, they permit a regurgitant stream to flow back into the left ventricle with a resultant murmur At the apex of the heart one may also hear the well known Austin Flint murmur, suggesting mitral stenosis, but this lesion merits little consideration because it is rarely associated with syphilitic aortic insufficiency As a matter of fact rheumatic valve disease is rarely associated with syphilitic aortic valves The writer has seen but two instances of mitral stenosis combined with syphilitic aortic insufficiency If there is clear clinical evidence of damaged heart valves other than the aortic, the case is in all probability not syphilitic aortitis

An interesting diastolic phenomenon is occasionally observed Replacing the usual diastolic murmur is a loud, buzzing sound, which may be so intense as to be heard by the unaided ear several feet from the patient s body Palpation over the sternum reveals an intense coarse, diastolic thrill These signs may appear suddenly, as happened in one of our patients after lifting a heavy weight The noise in the chest was so disturbing that it interfered with the individual s sleeping until he became accustomed to it Such cases seen by the writer have shown at autopsy an eversion of one or more aortic cusps Extending horizontally about midway up the body of the leaflet was a band of fibrous tissue which acted as a hinge During diastole the free margin of the leaflet everted and vibrated in the regurgitant stream of blood producing the diastolic thrill and murmur The writer also has seen several patients in whom syphilitic aortic insufficiency appeared suddenly with marked symptoms of dyspnea palpitation, edema etc Death from heart failure usually followed in a short time and at autopsy a recent rupture of one or more aortic cusps from their attachment at the commissure was found

With the development of free aortic regurgitation the X ray findings become fairly characteristic The left median distance is increased, the apex is rounded and elevated from the diaphragm, the heart is in the transverse position giving the so called shoe shape, and the pulsations are forceful The aortic shadow is broad and usually exceeds the spine and cava shadow on the right

Symptoms and Clinical Course — Since the majority of patients suffering from syphilitic aortic insufficiency ultimately develop myocardial failure, the symptoms in a given case will depend to a large extent on the ability of the heart to compensate for the lesion Breathlessness and palpitation on exertion may be the only symptoms and some patients are able to do light work for

several years On the other hand in an experience covering more than 100 autopsied cases of syphilitic aortic insufficiency the writer was impressed by the abrupt onset of symptoms and the progressive nature of the cardiac failure The following account is typical A well developed male between 30 and 50 with a negative cardiac history always able to do hard work observes that he is becoming unduly short of breath and that his heart beats more forcibly than usual These symptoms gradually increase over a period of weeks or months until the patient is no longer able to be up because of breathlessness or until edema of the feet appears Usually at this stage he is taken to the hospital and one finds the cardinal signs of congestive heart failure with an enlarged left ventricle and free aortic regurgitation In spite of treatment the patient may gradually fail or he may make a temporary recovery, but in a few weeks or months again develop signs of congestive failure Once more he may recover only to fail again in a still shorter period A frank decompensation in a patient with syphilitic aortic insufficiency signal the beginning of the end No patient seen by the writer has survived more than two years and the majority have died in less than one year from the first cardiac breakdown

This progressive heart failure is sufficiently striking compared to other types of heart disease to merit some consideration of the factors involved in the heart s exhaustion Many patient fail to recover from their first decompensation We have seen that the anatomical changes caused by syphilis at the aortic orifice lead ultimately to functional insufficiency While the leak is still small perfect compensation may be established But from the very nature of the pathological changes the functional lesion tends to be a progressive one and developing rapidly, it throws an insuperable burden on the heart which can not keep pace in establishing compensation

It is maintained by some writers that syphilis frequently invades the myocardium causing characteristic histological changes The writer was not able to substantiate this view from microscopic studies of a series of hearts showing syphilitic aortic insufficiency Fibrosis of the muscle cloudy swelling segmentation infiltration with lymphoid and other mononuclear cells were seen In eight instances the combination of fibrosis cellular infiltration and mucoid comparable to the histological picture of syphilitic myocarditis as described by Warthin was observed A careful search for spirochetes in the myocardium was made but not any were found Such myocardial changes as were noted were indistinguishable from those seen in hypertrophied hearts from other causes and to attribute them to syphilis appears unwarranted Even assuming that the myocardial lesions were due to syphilis it is impossible to estimate their functional significance Certainly the vast majority of patients with syphilitic aortitis have no signs of myocardial embarrassment until the root of the vessel is involved This is a vital point so far as the heart is concerned

If, on the other hand, myocardial syphilis was as frequent as some believe, we should see more instances of syphilitic heart disease in individuals who show at autopsy no involvement of the aortic orifice

We have considered thus far insufficiency of the aortic orifice and occlusion of the coronary arteries as factors influencing the clinical course of individuals suffering from syphilis at the root of the aorta Singly or in combination these impediments must seriously handicap the heart, and disposed by their nature to progress they appear to be the most important factors determining prognosis For all practical purposes, therefore, cardiac syphilis means syphilitic aortitis involving the root of the aorta

Prognosis and Treatment — The prognosis in syphilitic aortic insufficiency after the appearance of frank cardiac decompensation is indeed gloomy, in spite of any treatment that may be employed As mentioned above, many patients never recover from the first cardiac breakdown and those that do are virtually invalids the rest of their lives Death may occur suddenly even after compensation is restored The treatment is that employed in any case of advanced cardiac failure It is only after definite improvement in the circulation occurs that anti syphilitic treatment may be started Mercury may be used first by mouth and later on by inunction or intramuscularly, together with the oral administration of iodides In the absence of myocardial symptoms, but with free aortic regurgitation, the patient may be treated somewhat more vigorously In addition to the mercurials and iodides intravenous arsphenamine may be used though cautiously beginning with small weekly doses of 0 05 grams and increasing to 0 1 0 15 0 2, etc until ten to twelve injections have been administered Just how effective treatment may be at this stage of the disease is difficult to determine from actual experience Some cases continue without myocardial symptoms for several years, others run a progressive downhill course in spite of treatment

Aneurysm of the Aorta

Syphilis is the cause of aortic aneurysm in such a high percentage of cases that we need only mention the other infections that occasionally attack the aortic wall, leading to dilatation Such instances are recorded following rheumatic fever typhoid influenza pneumonia erysipelas and scarlet fever Rarely the aorta may be involved by direct extension from endocarditis of the aortic cusps but the patient usually succumbs to infection before the aorta undergoes much dilatation Mycotic aneurysms commonly associated with recent mitral or aortic endocarditis are seen occasionally Infected emboli probably gain entrance through the vasa vasorum causing a patchy mesaortitis and ultimate weakening of the aortic wall

Simple arteriosclerosis of the aorta rarely produces aneurysm Indeed the most extreme atheromatous changes are seen in the aorta rendering it a rigid calcified tube without the presence of aneurysm On the other hand syphilis and atheroma are frequently associated particularly in the individuals beyond forty

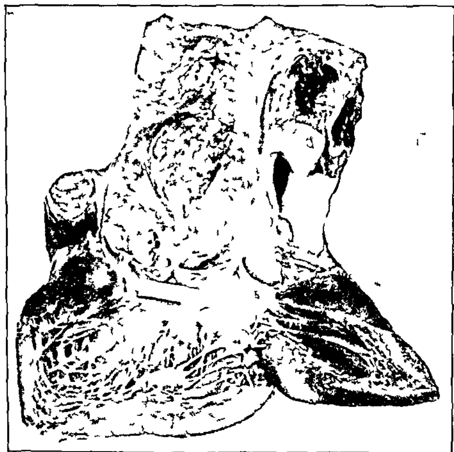


FIG 9 —Showing a syphilitic aorta also the seat of marked arteriosclerosis. Note the syphilitic lesions of the commissure

five In such instances the arteriosclerotic changes may obscure so completely those of syphilis that a trained pathologist will be unable to make a diagnosis without a microscopic examination Under such circumstances the region of the commissure should be carefully inspected for the characteristic lesion described above This is seen in Fig 9 which shows the aorta the seat of

advanced arteriosclerotic changes but with the typical lesion of syphilis at the commissures

In the discussion of syphilitic aortitis we saw that one result of the inflammation in the aorta was a scarring of the media The elastic lamina is destroyed and replaced by fibrous tissue, a process which seriously undermines the aortic wall At the site of the weaker areas the wall gives way and we have the early stage of aneurysm formation Depending on the distribution of the damaged areas we have different types of aneurysms A widespread and more or less uniform involvement of the media may lead to a diffuse dilatation of the whole vessel from the sinuses of Valsalva to the bifurcation of the iliac arteries Again the process may be fairly well confined to one part of the aorta, more commonly the ascending arch which may dilate to form a tumor that fills nearly half of the thorax This is the cylindrical or fusiform type of aneurysm The more common form, the sacculated aneurysm, originates from a localized area of weakness on one side of the aortic wall Here the aneurysmal sac may communicate with the main channel through a small or through a larger opening, depending to a large extent on the size of the area in the wall which originally gave way Thus we see that the irregular distribution of the syphilitic changes in the aorta causes a variety of architectural distortions in the wall of the vessel

The roentgenological diagnosis of aneurysm is important because the size and location can be determined so accurately Not infrequently a large aneurysm is first demonstrated by the X ray and the changes in the lungs which clinically were considered primary are shown to be secondary In general it can be said that aneurysms contrast sharply with their environment and usually have a smooth rounded border Occasionally hæmorrhage into the wall of the sac or neighbouring structures will cause a blurring of the outline Pulsations are frequently present and of course are usually expansile in type Their absence however, is common, especially when hæmorrhage into the surrounding structures has occurred or in the presence of a clot within the sac Occasionally from a single examination the roentgenologist can not distinguish between a tumor and an aneurysm Such a case must await comparison plates Frequently a thoracic mass which has the appearance of an aneurysm on the plate can be shown by fluoroscopy to be separate from the great vessels

For descriptive purposes the thoracic aorta is divided into ascending, transverse, and descending portions

Aneurysm of the Ascending Aorta

Involvement of this part of the aortic arch is very often associated with insufficiency of the aortic valve either from ring dilation, from diseased aortic

leaflets or from both Also the coronary arteries may be occluded when anginal symptoms are often prominent Thus the clinical picture may show nothing to suggest aneurysm but only heart disease If the sac is small and



Fig 10 — Showing an aneurysm of the ascending arch involving the aortic ring leading to free aortic regurgitation The valve cusps are not involved

near the root of the aorta it may be impossible to make the diagnosis by any means at our disposal The first symptoms may be dyspnea and objectively

we find the usual signs of free aortic regurgitation Death comes from congestive heart failure in the majority of such cases An example of aneurysm of the ascending arch involving the aortic ring causing free aortic regurgitation



FIG 11 — Showing the site of rupture of an aortic aneurysm into the pulmonary artery

and death from heart failure is shown in Fig 10 If on the other hand the aortic orifice is not caught in the process, a large saccular or fusiform aneurysm

may be present with no evidence of heart disease Here the physical signs are often more conspicuous than the subjective symptoms although pain may be an outstanding feature There is percussion dullness to the right of the sternum in the second and third inter paces A more or less vigorous pulsation may occur over the tumor depending on the amount and degree of organization of the clot in the sac wall Large aneurysms with little or no pulsation may be mistaken for new growths Occasionally the superior vena cava is com pressed, causing a striking distension of the superficial veins of the head neck, arms and upp r thorax When large the sac may erode the ribs and sternum and destroy the sterno-clavicular joint Rupture may occur into the lung right bronchus pericardium superior vena cava or right auricle Rarely does rupture occur externally The writer has seen three instances of aneurysm of a sinus of Valsalva which projected anteriorly and ruptured into the pulmonary artery (See Fig 11) In each instance the patient was well until the time of rupture and all died of heart failure in from one to three weeks The outstand ing clinical features were sudden onset of marked respiratory distress an unusually intense thrill throughout the cardiac cycle felt best over the conus of the right ventricle and a loud rasping murmur with a systolic and diastolic accentuation heard over the pulmonary artery and transmitted toward the left shoulder

Aneurysm of the Transverse Aorta

Aneurysms of this portion of the aorta even when small are more likely to produce symptoms from compression of contiguous structures Tumors too small to be demonstrable by physical signs may cause the most severe symptoms or even death The trachea just above the bifurcation may be com pressed and death come from suffocation In two instances seen by the writer the patients toward the end were compelled to keep the trachea stretched continuously by bending the head up The relief afforded by this position was apparent from the autopsy findings By pulling the trachea taut the aneu rysmal sac was pushed aside Erosion of the spine with compression of the spinal cord is sometimes seen

Pulmonary symptoms from compression of the lung or bronchus may be conspicuous and fatal Hæmoptysis or expectoration of bloody sputum may suggest tuberculosis

If the aneurysmal sac bulges forward and upward it may be seen as a pulsating tumor In less obvious cases an abnormal impulse and impact may be palpated over the manubrium sterni or in the supra sternal notch An increased area of dullness may be elicited anteriorly more rarely posteriorly near the spine The mouths of the arteries from the arch may be caught in

the aneurysmal pouch, causing a disparity in the pulse volume in the carotids or in the radial arteries Rupture may occur into the trachea, bronchus, lung, mediastinum or œsophagus

Aneurysm of the Descending Aorta

In this portion of the aorta, aneurysms may attain enormous size before symptoms occur They may be discovered by X ray, or at post mortem in cases of sudden death from internal rupture A characteristic symptom is pain of an agonizing character This appears in the back in the region of the left scapula and may follow the distribution of the intercostals to the front of the body Later the nerve roots may be severed, pain disappears, and the skin becomes anesthetic over the affected area Pressure of the sac may compress the left bronchus and cause collapse of the lung The resulting diminution in vital capacity produces dyspnea on exertion, which may be an early symptom. Pneumonia developing in the collapsed lung is frequently the cause of death in such cases Elevation of the larynx may reveal a downward pull with each heart beat the so called tracheal tug Pressure on the left recurrent laryngeal nerve may cause paroxysmal attacks of dyspnea, and later change in the voice from adductor paralysis The voice becomes weak, hoarse, with a peculiar cracked quality Sometimes it is reduced to a whisper but actual aphonia is rare An irritative cough is common and with adductor paralysis it becomes ringing or ' brassy, the so-called aneurysmal cough Rarely the sympathetic fibers to the head and neck are compressed causing dilatation of the pupils and flushing of the face Dysphagia may be an early symptom Fatal hæmorrhage may result from rupture into the œsophagus

Aneurysm of the Abdominal Aorta

This is a rare site for aneurysms The sac may show little or no expansile pulsation and, as an abdominal tumor, be difficult to diagnose The most characteristic symptom is pain and of a type similar to that seen in aneurysm of the descending aorta Early, the pain may be paroxysmal in nature, later an intense agony when the aneurysm erodes the spine Most commonly rupture occurs into the retro-peritoneal space and in some instances the clinical picture may be that of an acute abdominal condition and the patient submitted to operation

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Dissecting Aneurysm of the Aorta

An uncommon but interesting affection of the aorta, unrelated to syphilis, is a spontaneous rupture of the intima permitting blood to pass into the wall of the vessel and dissect its coats hence the designation dissecting aneurysm Although first described by Maunoir in 1802, the various pathological aspects of the affection became firmly established by the careful observations of Peacock in 1843 The most recent and thorough survey of the subject is contained in a monograph by Sheenan who analyzed 300 cases of dissecting aneurysm of the aorta including 17 of his own He found that a correct ante mortem diagnosis had been made in only 6 cases That a correct clinical diagnosis is not made more often may be explained by the fact that many patients die suddenly or are so ill, when first seen that a satisfactory history is not obtainable and a thorough examination which may afford a clue to the diagnosis is impossible However it seems to the writer that too much stress has been placed on the difficulty of the diagnosis and that the signs and symptoms of dissecting aneurysm often are sufficiently characteristic to make the diagnosis relatively easy Just as coronary thrombosis is now, after some twenty years generally recognized it seems likely that as the clinical picture of dissecting aneurysm of the aorta becomes widely known, a correct ante mortem diagnosis will be made more often

Pathology and Pathogenesis

The gross appearance of the intima of the aorta, particularly in young patients may exhibit little or no change, whereas in older people varied degrees of simple intimal arteriosclerosis are found

At the root of the aorta from 0 5 to 3 cm or more above the aortic valve there is often a rent in the intima from 0 25 to 2 or 3 cm in length which runs transversely to the channel of the aorta The tear may be irregular or as often happens, it may be sharp with its edges appearing as if made by a knife Less common sites of rupture are found at the junction of the ascending and transverse aorta and at the junction of the transverse and descending aorta Often the tear in the intima is at a site showing the least intimal change In the majority of cases the tear extends into the media and the dissection occurs between the middle and outer thirds of this coat involving from one half to two thirds of the circumference of the vessel The extent of the dissection varies widely In some cases the entire length of the aorta including the iliac arteries is involved and almost any artery coming directly off the aorta may be caught in the process In tears near the root the dissection often extends downward toward the aortic ring causing a high degree of aortic insufficiency due to

distortion of the architecture of the valve area and in a few cases there is more or less narrowing of the coronary ostia An outward perforation of the adventitia may occur at any point along the aortic wall If near the heart the hemorrhage usually is into the pericardial sac if farther along the aorta it will be into the pleural cavity most often on the left rarely into the abdominal cavity Occasionally the dissection may extend a certain distance and perforate into the natural aortic lumen causing the so-called double barrelled aorta Since the media is the supporting structure of the aortic wall it is not surprising that medial disease should precede the development of dissecting aneurysm

Except in rare cases in which an atheroma with ulceration happens to lie immediately adjacent to the diseased media there is no evidence to prove that intimal lesions play a significant role in the occurrence or localization of the rupture The medial lesion most often encountered is a focal or diffuse mucoid or hyaline degeneration often leading to cyst formation These changes usually are most severe in the vicinity of the tear and not often associated with inflammatory changes or with significant intimal sclerosis The medial lesions were carefully studied by Erdheim who called them medio-necrosis aortæ idiopathica cystica

The etiology of this type of medio-necrosis which has been observed in the majority of cases of dissecting aneurysm is not known Less obscure is the occasional case of medial degeneration which is associated with obliteration of the vasa vasorum either by arteriosclerosis or by a low grade inflammatory process From a study of such cases Tyson believes that the diseased vasa vasorum may rupture causing a hematoma which splits the medial coat Under these circumstances the tear in the intima would not be a necessary factor in the formation of an aneurysm As the source of capillary bleeding cannot always be found in a histological study it seems reasonable to assume that in some cases at least hemorrhage into the diseased media might occur with formation of a hematoma even while the small vessels in this region exhibit no demonstrable histological changes Despite the obscurity regarding the etiology of the medial lesions it is recognized generally that they are primarily responsible for the development of dissecting aneurysm of the aorta As the limit of extensibility of the intima is exceeded it tears and as this limit is apparently less than that of the outer coat of the media the actual rupture is sub total and conditions for dissection occur

Dissecting aneurysm of the aorta is not a common affection Estimates of its occurrence vary from 1 to 00 to 1 in 500 autopsies Males are affected more often than females in the proportion of about two to one A majority of cases appear in the later decades of life although Klotz and Simpson collected 42 cases under forty of which 21 were juveniles and 7 adolescent

Signs and Symptoms

The commonest symptom is chest pain which usually is sudden and intense It is often substernal and radiates to the back into the abdomen or lower extremities but rarely into the upper extremities Sometimes it appears first in the interscapular region or in the abdomen Characteristic of the pain of dissecting aneurysm is its persistence Although temporarily relieved by morphine it tends to recur and often is more or less constant from its inception until the patient dies The patient usually is more or less dyspneic and appears acutely ill Some are quite restless others sometimes are prostrated and apparently in shock although the blood pressure may be well above normal Cyanosis of the face and neck from obstruction of the venous return may be present but pallor also has been observed

There is nothing characteristic about the pulse, it may be fairly normal in some cases, in others irregular due to the occurrence of extra systoles or auricular fibrillation When the aortic orifice is deformed by the dissecting column of blood the pulse is of the water hammer type Varying grades of tachycardia up to 140 may be present In patients beyond forty hypertension is the rule and in many an elevated pressure has antedated by years the appearance of a dissecting aneurysm

The objective evidence of heart disease varies widely and affords little assistance in the diagnosis The heart may or may not be enlarged the sounds may be normal or quite feeble If hypertension is present, an apical systolic murmur and an accentuated tympanitic aortic second sound may occur A to-and fro murmur of free aortic regurgitation may be present A gallop rhythm has been noted in a few cases A low grade fever and leucocytosis often are present for a few days following the onset There are no characteristic deformities in the electrocardiogram With secondary rupture into the pericardial sac ST deviations and negative T waves appear The x ray findings may be equivocal or they may show a deformity of the cardiac aortic shadow which may increase rapidly in size

Diagnosis Prognosis and Treatment

The cardinal aspects of the clinical picture of dissecting aneurysm in the usual case may be given as follows A male beyond forty years of age and known to have had arterial hypertension is seized suddenly with agonizing pain radiating widely both to the front and to the interscapular region sometimes into the abdomen and legs but rarely into the arms Pain appearing first under the sternum then in the back and shortly in the abdomen is very suggestive of dissecting aneurysm Persistent pain for hours or days is note-

worthy Although temporarily relieved by full therapeutic doses of morphine the pain reappears perhaps as agonizing as ever

Physical examination of a patient with a dissecting aneurysm of the aorta reveals little more than a very ill apprehensive patient who has a rapid and enlarged heart Fever and leucocytosis appear and the electrocardiogram is not characteristic of myocardial infarction

The patient fails steadily and dies in a few hours or days after the onset of the attack If while under observation the patient has pain in the region of the lower extremities and no palpable pulse of the femoral arteries the diagnosis is almost certain Since death usually results from hemorrhage into the pericardial or pleural cavity clinical evidence pointing to these complications supports the diagnosis

The *condition most likely to be confused* with dissecting aortic aneurysm is coronary thrombosis with infarction of the heart wall A distinction of course cannot be made in patients who die suddenly or who are moribund when first seen

However, in those who survive the initial attack the following points may aid in establishing the correct diagnosis

(1) Pain in dissecting aneurysm is more severe more sudden in onset has a wider radiation rarely extends to the arms and is more likely to be persistent than is the pain of coronary thrombosis

(2) Syncope often occurs in the initial attack of dissecting aneurysm rarely in coronary thrombosis

(3) Shock may occur with a normal or elevated blood pressure in dissecting aneurysm whereas shock in coronary thrombosis is associated with a fall in blood pressure

(4) In myocardial infarction serial electrocardiograms usually show characteristic deformities which are not found in dissecting aneurysm

(5) The majority of patients with coronary thrombosis survive the initial attack whereas only about one out of four patients with dissecting aneurysm survive the initial attack

The *prognosis* in a patient with dissecting aneurysm is admittedly grave As some patients die before they are seen by a physician dissecting aneurysm must be considered as one cause of sudden death found by the medicolegal examiner The majority of patients succumb a few hours or days after the onset of symptoms while in the rare case in which secondary rupture occurs back into the aortic lumen the patient may survive for months or even for years to die of some unrelated cause

Treatment is directed toward keeping the patient as comfortable as possible with full therapeutic doses of opiates and such measures as may relieve him of any emotional or physical strain

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CHAPTER XIV-B

ANGINA PECTORIS AND CORONARY THROMBOSIS (CARDIAC) INFARCTION

By FRED M SMITH

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CORONARY THROMBOSIS (CARDIAC INFARCTION)

PART I

ANGINA PECTORIS

Definition — Angina pectoris is a syndrome in which the pain is the characteristic feature. The pain is identified by the paroxysmal occur

rence character distribution and the fact that generally it is precipitated by factors which increase the demands on the heart It usually appears with exercise or excitement generally is felt first over the sternum or heart frequently transmitted to the left shoulder or arm occasionally to the right shoulder or arm or perhaps to the neck and head and except in the more severe form disappears within a few minutes after the exercise is discontinued or the excitement subsides

Incidence

The incidence parallels that of coronary artery disease and is greatest between 50 and 65 years of age The disorder occasionally occurs in the age period between 30 and 40 and in rare instances is observed in younger individuals It is four to six times more common in the male sex There is a general belief that the incidence is particularly high in the business and professional groups However in the series of coronary artery disease studied by Levy and his coworkers[1] the highest percentage 29 and 28 per cent respectively occurred in housewives and manual laborers It was interesting to note that clerical workers came next with incidence of 21 per cent whereas the group composed of foremen and skilled laborers and that of professional men and executives each constituted 18 per cent Levy cited the report by Kleinmann in which similar observations were recorded The results of these studies indicate that coronary artery disease occurs in all classes and that in the presence of the condition excess physical or mental strain promotes the appearance of cardiac pain

Pathology

Arteriosclerosis of the coronary arteries which ordinarily is extensive with partial or even complete occlusion of one or more of the main branches is the most common pathological alteration When angina pectoris occurs with syphilitic aortitis there is usually encroachment on or occlusion of the orifices of one or both coronary arteries Thus in 69 cases of syphilitic aortitis studied by Pincoffs and Love cardiac disease was responsible for death in 21 Of these 21 there were 15 in which one or both ostia of the coronary arteries were stenosed In these anginal pain was the most common complaint occurring in 13 Death was sudden and unexpected in 10 Paroxysmal dyspnea was also a prominent feature Among the above 21 cases there were 15 with aortic insufficiency However in the 6 that did not present obstruction of the orifices

of the coronary arteries there was only one that had pain suggestive of angina pectoris

Keefer and Resnik[3] collected a series of 386 cases from the literature which came to necropsy and added 13 of their own Sclerosis of the coronary arteries was reported in 388 of the total 399 cases It was pointed out that in the instances of angina pectoris not associated with coronary artery disease aortic insufficiency was the predominating lesion and that in the vast majority of cases it was secondary to syphilitic aortitis These findings are in general accord with those of others Thus Polanco[4] analyzed the symptoms in a series of 242 cases of coronary artery disease that came to necropsy There was history of angina in 36 instances In 33 the arteriosclerotic process was advanced and in the remaining 3 of moderate grade History of pain was not obtained in those presenting minor alterations in the coronary vessels In the 34 cases reported by Saphir and his coworkers[5] there were 18 that gave a history of angina It was stated that a number of these presented coronary thrombosis arteriosclerotic occlusion and myocardial infarction There were others however with the same pathological changes from whom no mention was made of pain Blumgart Schlesinger and Davis[6] in a more recent investigation have made a detailed study of the pathological findings in coronary artery disease and their relation to the clinical manifestations There were 12 cases in which angina pectoris was uncomplicated and the primary condition Ten of these had old complete occlusion of at least two main coronary arteries In 3 the three main branches had been obstructed Moreover in the remaining 7 the only unoccluded main vessel was markedly narrowed Furthermore in the 2 hearts of the group in which only one of the main coronary arteries was closed the other two were partially obstructed There were also 5 cases in which the angina was associated with other conditions Of these 3 had advanced rheumatic valvular disease and 1 cor pulmonale These presented relatively few occluded vessels Attention was called to the additional load imposed on the heart by the associated conditions These observers concluded that the presence or absence of pathological changes in the coronary arteries are not always the sole factor determining the presence or absence of angina pectoris

Angina pectoris is observed occasionally in the rheumatic type of aortic valve disease and has been noted in various other conditions such as arteriovenous aneurysm high grade anemia hyperthyroidism hypothyroidism and paroxysmal tachycardia A careful analysis of these conditions discloses that various factors add to the demands on the heart or render it less efficient However in most instances it is doubtful

rence, character, distribution, and the fact that generally it is precipitated by factors which increase the demands on the heart. It usually appears with exercise or excitement, generally is felt first over the sternum or heart, frequently transmitted to the left shoulder or arm, occasionally to the right shoulder or arm, or perhaps to the neck and head, and except in the more severe form disappears within a few minutes after the exercise is discontinued or the excitement subsides.

Incidence

The incidence parallels that of coronary artery disease and is greatest between 50 and 65 years of age. The disorder occasionally occurs in the age period between 30 and 40 and in rare instances is observed in younger individuals. It is four to six times more common in the male sex. There is a general belief that the incidence is particularly high in the business and professional groups. However, in the series of coronary artery disease studied by Levy and his coworkers[1] the highest percentage, 29 and 28 per cent, respectively, occurred in housewives and manual laborers. It was interesting to note that clerical workers came next with incidence of 21 per cent, whereas the group composed of foremen and skilled laborers and that of professional men and executives each constituted 18 per cent. Levy cited the report by Kleinmann in which similar observations were recorded. The results of these studies indicate that coronary artery disease occurs in all classes and that in the presence of the condition excess physical or mental strain promotes the appearance of cardiac pain.

Pathology

Arteriosclerosis of the coronary arteries, which ordinarily is extensive with partial or even complete occlusion of one or more of the main branches, is the most common pathological alteration. When angina pectoris occurs with syphilitic aortitis there is usually encroachment on or occlusion of the orifices of one or both coronary arteries. Thus in 69 cases of syphilitic aortitis studied by Pincoffs and Love[2] cardiac disease was responsible for death in 21. Of these 21 there were 15 in which one or both ostia of the coronary arteries were stenosed. In these anginal pain was the most common complaint, occurring in 13. Death was sudden and unexpected in 10. Paroxysmal dyspnea was also a prominent feature. Among the above 21 cases there were 15 with aortic insufficiency. However, in the 6, that did not present obstruction of the orifices

of the coronary arteries there was only one that had pain suggestive of angina pectoris

Keefer and Resnik[3] collected a series of 386 cases from the literature which came to necropsy and added 13 of their own Sclerosis of the coronary arteries was reported in 388 of the total 399 cases It was pointed out that in the instances of angina pectoris not associated with coronary artery disease aortic insufficiency was the predominating lesion and that in the vast majority of cases it was secondary to syphilitic aortitis These findings are in general accord with those of others Thus Polanco[4] analyzed the symptom in a series of 242 cases of coronary artery disease that came to necropsy There was history of angina in 36 instances In 33 the arteriosclerotic process was advanced and in the remaining 3 of moderate grade History of pain was not obtained in those presenting minor alterations in the coronary vessels In the 34 cases reported by Saphir and his coworkers[5] there were 18 that gave a history of angina It was stated that a number of these presented coronary thrombosis arteriosclerotic occlusion and myocardial infarction There were others however with the same pathological changes from whom no mention was made of pain Blumgart Schlesinger and Davis[6] in a more recent investigation have made a detailed study of the pathological findings in coronary artery disease and their relation to the clinical manifestation There were 12 cases in which angina pectoris was uncomplicated and the primary condition Ten of these had old complete occlusion of at least two main coronary arteries In 3 the three main branches had been obstructed Moreover in the remaining 7 the only unoccluded main vessel was markedly narrowed Furthermore in the 2 hearts of the group in which only one of the main coronary arteries was closed the other two were partially obstructed There were also 5 cases in which the angina was associated with other condition Of these 3 had advanced rheumatic valvular disease and 1 cor pulmonale These presented relatively few occluded vessels Attention was called to the additional load imposed on the heart by the associated conditions These observer concluded that the presence or absence of pathological changes in the coronary arteries are not always the sole factor determining the presence or absence of angina pectoris

Angina pectoris is observed occasionally in the rheumatic type of aortic valve disease and has been noted in various other conditions such as arteriovenous aneurysm high grade anemia hyperthyroidism hypothyroidism and paroxysmal tachycardia A careful analysis of these conditions discloses that various factors add to the demand on the heart or render it less efficient However in most instances it is doubtful

whether the angina would have occurred had these conditions not been supplemented by coronary artery disease as illustrated by the following case

A man 58 years of age consulted the writer because of pain in the chest extending to the left shoulder and arm precipitated by exertion or excitement These attacks had persisted despite a period of several months rest and he was obliged to give up his work as a salesman After talking with this man it was apparent that he had been on edge and easily upset This was confirmed by the wife There was no demonstrable increase in the size of the thyroid gland but the general appearance the temperature of the skin moderate increase in the pulse rate and the blood pressure readings pointed to an increase in the metabolic rate which was verified later A subtotal thyroidectomy was performed following which the anginal attacks disappeared This patient had no further trouble until four years later when he returned to the hospital because of paroxysmal nocturnal dyspnea which followed coronary thrombosis He recovered and since then has been free from cardiac symptoms for more than a year

Mechanism of Anginal Pain

Many theories have been advanced for the explanation of angina pectoris In the vast majority of cases however the disorder is associated with disease of the aorta or of the coronary arteries or perhaps of both of these structures Consequently the two most favored hypotheses have pertained to these conditions Wall and Corrigan and later Allbutt, Vaquez and Wenkebach ascribed the syndrome to a disease of the aorta Vaquez[7] in discussing the question emphasized the frequency with which obstructive lesions are associated with angina pectoris but argued that this is merely a special localization of a super sigmoid aortitis He furthermore points out that the nerve filaments that pass from the aorta to the cardiac plexus are particularly abundant in the initial portion of the coronary arteries especially at the orifices

Jenner is given credit for being the first to connect angina pectoris with disease of the coronary arteries This theory was supported later by Hunter Burns Potain Huchard and others Burns in particular anticipated some of the more recent ideas relative to the mechanism of the pain The developments during the past twenty years have focused attention again on the coronary arteries The first of these developments was the identification of the syndrome of coronary thrombosis[8, 9] This was followed by investigation in which pain was induced by the experimental ligation of the coronary arteries in the dog[10, 11], observations on the effect of temporary obstruction of the blood supply to the extremities[1] electrocardiographic studies in which it was noted that changes of a transient

nature similar to those associated with coronary thrombosis may occur during attacks of angina pectoris[13 14 15] and finally the studies in which attacks of angina were induced or prevented by breathing air of reduced or increased oxygen content[16 17] The results of these various investigations have fully convinced most of those interested in the field that a deficient blood supply to the myocardium is the essential cause for the angina in the overwhelming majority of cases There is still a difference of opinion as to whether the condition results from anoxemia the accumulation of metabolites or from some other factor

On the basis of this conception it may be assumed that under normal conditions the blood supply to the various sections of the myocardium is ample to meet the needs If however it is diminished to a certain area the efficiency of that section is reduced Thus this area of the myocardium may be overtaxed by a load that is well within the functional capacity of the remaining cardiac musculature and pain may result This is referred to commonly as transient insufficiency of the coronary circulation It ordinarily results from the partial or complete obstruction of one or more of the coronary vessels

It is well recognized that disease of the coronary arteries is not responsible for all cases of angina pectoris Moreover the extent of the involvement necessary for the production of the syndrome probably is much less when the heart is handicapped from other causes Mention has been made of syphilitic aortitis In this condition the encroachment on the orifices of the coronary arteries is no doubt an important factor There are instances however such as rupture of the aorta and dissecting aneurysm in which it would seem that disease of the aorta alone may be the basis of the anginal pain Furthermore cases have appeared in the literature such as reported by Leary[18] in which there was no demonstrable disease of either the aorta or the coronary arteries One may well speculate on how often this would obtain if the coronary vessels were examined carefully by injection methods such as employed by Schlesinger[19] Isolated lesions capable of producing a relative insufficiency of the circulation to the myocardium readily may be overlooked Cases such as recorded by Leary have directed attention to other possibilities and of these increased vasomotor tone or spasm has received increasing support in recent years The association of indigestion with angina pectoris suggesting reflex *connection between the heart and the stomach* esophagus and gall bladder is a common observation Von Bergmann[20] reports that the inflation of a balloon in the stomach of the dog produces vasoconstriction of the coronary arteries which is abolished by atropine or section of the vagus These results have been confirmed by Gilbert Fenn

and LeRoy[1] Morrison and Swalm have carried out similar experiments on two patients with angina pectoris In both pain was produced and in one there was pronounced reduction in the cardiac rate The distress promptly disappeared following the release of the pressure within the balloon

The receptive state of the sensory nerve endings or of the nervous mechanism in general is another factor which may determine the presence or absence of anginal pain Katz Mayne and Weinstein[3] have demonstrated in the dog that if the nerves accompanying a coronary artery are blocked the obstruction of the vessel apparently does not cause pain Furthermore stimulation of the nerves seems to produce the same reaction as the ligation of the vessel and the surrounding structures Finally it is generally known that there is great variation in the individual response to pain[4] Roberts[5] has stressed this factor in angina and believes that it is largely responsible for the low incidence of this disorder in the negroes

Symptoms

There is a remarkable variation in the character extent and distribution of pain At the onset there may be no more than a mild uneasiness or an indefinite sense of discomfort or perhaps a burning sensation in the substernal region with excitement or with exercise such as walking uphill Later it is commonly described as heaviness fullness or a constricting sensation which may become so severe that the individual is obliged to stop because of the fear that it may become even more intense or perhaps that something might happen The pain is felt usually over the sternum or cardiac area and not infrequently over the lower substernal region possibly extending to the epigastrium In rare instances it is confined entirely to the upper abdomen

The distress commonly appears after meals especially with exercise and is often associated with a feeling of fullness in the epigastrium and the consciousness of the presence of gas Under these circumstances the individual usually attributes his condition to indigestion and it may be difficult to convince him otherwise The association with meals and the fact that the distress frequently is relieved by eructation of gas suggests that increased gastric tension is the precipitating factor and that the effects on the heart result from reflex stimulation of the vagus

Later in the course of the disorder there is a tendency for the pain to involve a larger area in the chest or to radiate to the arm neck jaw perhaps the head and occasionally the back It is transmitted more

frequently to the left shoulder and with increase in intensity down the arm on the ulnar side to the elbow or fingers The distress in the latter location often is described as a numbness or feeling of constriction In the more severe form the pain may be referred to the right shoulder and arm The pain in some is felt first in the arm shoulder and in rare instances the neck jaw or pharynx and later extends to the chest Occasionally the distress at some peripheral point so dominates the picture that the possible associated involvement of the chest is overlooked Thus patients have been treated for neuritis of the arm arthritis of the shoulder had teeth extracted or were subjected to operations on the throat Even though the pain may vary in character and have a wide range of distribution it is always constant in a given individual except for degrees of intensity and extent of radiation Furthermore the attacks except in the more severe form when there is always a question of coronary thrombosis invariably are precipitated by factors which increase the demand on the heart Thus the possible exciting factors are numerous and in the more severe form may not be apparent but are more commonly of some type of physical activity particularly walking excitement or overdistention of the stomach from food and associated accumulation of gas The effects from walking are more evident in cold weather against a strong wind or with a full stomach In some instances pain awakens the individual from sleep When not due to coronary thrombosis it is attributed usually to increased blood pressure and accelerated cardiac rate incident to nightmare and other forms of sleep disturbances It is important to bear in mind that the attack particularly during the early stages generally subsides within a few minutes after the exciting factor is eliminated In the beginning the attacks often occur at infrequent intervals and may be absent for a period of weeks or even months It is a common experience that the individual may be able to do more at one time than at another without precipitating an attack Moreover after he is once warmed up he may be able to continue his physical activity or even extend it without experiencing discomfort As time goes on however the attacks commonly are precipitated more easily and last longer In the still more advanced stage they may occur spontaneously during periods of rest and complete relaxation

Objective Findings

It is apparent from the foregoing discussion that angina pectoris may be associated with varying degrees and types of cardiac damage Not infrequently however there are no demonstrable structural alterations

in the heart A roentgenological examination and Wassermann test are indicated if the possibility of syphilis is suspected Because of the frequent association with advanced disease of the coronary arteries presenting arteriosclerotic occlusion thrombosis and cardiac infarction alterations are commonly observed in the electrocardiogram These pertain to changes in the Q R S group the R S-T segment and the T wave and will be discussed more in detail in connection with coronary thrombosis They may represent the permanent effects from cardiac infarction or perhaps result from the gradual replacement of cardiac muscle by fibrous tissue If there has been a recent infarct serial curves usually will disclose consecutive alterations Electrocardiograms taken during attacks may record abnormalities involving the R S-T segment and the T wave of a transient nature similar to those associated with coronary thrombosis

Diagnosis

The typical form of angina pectoris is recognized readily In general the unusual location of the pain or perhaps the trifling nature of the distress and the absence of definite physical signs are responsible for the mistaken diagnosis The possibility of angina pectoris should be considered always in every individual of the arteriosclerotic age with pain in the chest epigastrium shoulder arm or neck The apparent localization of the pain at some peripheral point has been mentioned A case was observed recently by the writer in which the pain was confined to the left shoulder In this instance the condition had been mistaken for arthritis Anderson[26] cites the account of several patients who had had teeth extracted because of pain in the jaw and mentions that of another who had consulted various otolaryngologists over a period of two and one half years because of a tight feeling in the throat The extension to or localization of the distress in the epigastrium and the frequent association with indigestion not infrequently is confusing Under these circumstances the distress commonly appears after meals and may suggest gall bladder disease malignancy or perhaps peptic ulcer In a case observed by the writer the distress was limited entirely to the epigastrium and usually occurred about one hour after the noonday meal A careful analysis of the story however disclosed that the so called indigestion invariably appeared while he was walking back to his office and promptly subsided with rest moreover the subsequent course confirmed the diagnosis of coronary artery disease It is well to bear in mind that angina pectoris may be associated with gall bladder disease peptic ulcer or other conditions of the upper abdomen As emphasized by the above

case a careful history with particular reference to the relation of the pain to factors which increase the demands on the heart ordinarily will exclude or determine definitely the presence of cardiac pain. Furthermore usually it will contribute valuable information concerning the other conditions mentioned.

Coronary thrombosis commonly precedes or follows the onset of angina pectoris. Thus when the pain is more severe and lasting than usual, occurs under unusual circumstances, particularly while the patient is at rest and especially when not relieved by nitroglycerin or amyl nitrite, the possibility of *coronary accident* should be considered seriously. It is well to bear in mind that the character and distribution of pain may be identical in the two conditions. In coronary thrombosis however the distress usually is more lasting and, instead of disappearing in a few minutes, may continue for hours or even days and perhaps persist in a minor form after hypodermic administration of morphine. Under the latter circumstances the diagnosis ordinarily is evident. The differentiation of angina pectoris from the less evident forms of coronary thrombosis however may be extremely difficult, yet it is most important from the standpoint of treatment. The association of shortness of breath is highly significant. The demonstration of acute structural alterations in the heart determines the diagnosis. Suggestive signs include the appearance of distant and poorly differentiated cardiac sounds, the occurrence of premature beats or the onset of auricular fibrillation. The appearance of gallop rhythm, systolic apical murmur or pericardial friction rub constitute conclusive evidence. Significant alterations usually are evident in the electrocardiogram and in doubtful cases may be the determining factor in establishing the diagnosis. However unless serial curves are taken these may escape attention. Moreover as previously pointed out transient changes not infrequently occur during attacks of angina pectoris. If there is any doubt regarding the diagnosis the individual should be given the benefit of a period of rest.

Hypertrophic arthritis of the spine is one of the most common causes of pain over the cardiac area or the left upper chest. Occasionally destructive lesions of the spine from various causes, herpes zoster or nerve root pressure from aneurysm, mediastinal or pulmonary tumor are responsible. In certain instances a few days observation with particular reference to the factors that precipitate or aggravate the pain may be necessary in differentiating a spondylitis from angina pectoris. With the various other disorders mentioned the history is different and this with the results from physical examination ordinarily directs attention to the probable diagnosis.

Pain over the cardiac area is common in *acute rheumatic heart disease* with or without pericarditis It is observed also not infrequently in *chronic valvular heart disease* In certain instances especially in aortic insufficiency or stenosis the pain has the characteristic aspects of angina Distress over the cardiac area is commonly associated also with premature contractions and other forms of *cardiac irregularities* With paroxysms of excessive heart rate particularly in auricular flutter or paroxysmal tachycardia it may be transmitted to the left shoulder and arm as in angina Finally discomfort over this region frequently occurs in hyper sensitive individuals in whom there is no demonstrable organic heart disease

Course and Prognosis

The outlook always is uncertain The reason is apparent from the advanced disease of the coronary arteries usually associated with this condition Coronary thrombosis with its varying results is common and if the effects on the heart are overwhelming sudden death occurs *Moreover sudden death may occur without coronary thrombosis* Thus the wife or some responsible member of the family should be informed regarding the possibilities Some ultimately pass into cardiac failure either because of the gradual progression of the arteriosclerotic process or perhaps because of coronary thrombosis and with this the pain frequently disappears

Fortunately there is a more favorable aspect which has been emphasized by the literature of recent years In a series of 500 cases reported by White and Bland [7] the average duration of life following the onset of the symptoms was 4 5 years in the 213 cases known to be dead and 5 1 years in the 273 cases still living Among this series 3 patients had had the disorder for over twenty years and one was still alive twenty one years after the onset Hart [8] in a plea for greater optimism in the prognosis of angina pectoris and coronary thrombosis cites instances from his own experience to justify his viewpoint and refers to his analysis of the case histories published by Sir James Mackenzie In 147 cases classified by Mackenzie as primary angina one man was still living thirty one years after his first attack and was still following his trade as a joiner three had lived twenty five years or more one twenty years seven fifteen years or more and twenty one ten years or more Wedd and Smith[29] from the study of 166 cases report that the average age at onset was 64 3 years The average duration of the condition was 5 8 years There were 26 15 7 per cent that lived ten years or longer

It was further pointed out that 70 per cent reached or exceeded the calculated life expectancy and that 48 per cent passed it by five or more years

The prognosis is determined to a certain extent by the condition of the cardiovascular system It is always serious in those with frequent and severe attacks regardless of the findings Furthermore the course usually is progressively downward in those with syphilitic aortitis The reason for this was indicated in the foregoing discussion The outlook in general is more favorable in the cases in which the attacks are of a mild nature occur at infrequent intervals and when it is not possible to demonstrate significant structural alterations in the heart The angina associated with thyrotoxicosis high grade anemia and arteriovenous aneurysm commonly is abolished by effective treatment of these conditions There are other factors such as the temperament of the individual that may influence the duration Thus in those with hypersensitive nervous systems the basic pathology necessary to the production of the pain may be considerably less than in the placid individual This is a recognized factor in women and also very probably is operative in thyrotoxicosis Finally the duration of life may be greatly influenced by the care with which medical advice is followed Years may be added whereas sudden death may result from the disregard of factors that precipitate the pain

Treatment

It is generally possible to benefit the individual with angina pectoris and oftentimes a great deal may be done The extent to which this may be accomplished however depends in a large measure on the care with which the physician analyzes the patient the condition of the cardiovascular system and all factors pertaining to the precipitation of attacks and in turn adopts measures to correct or alter the situation Rest is one of the most effective means of restoring the cardiac function however usually it is not necessary to confine the subject to bed In the milder form curtailment in the exercise alone may produce a marked improvement Thus a reduction in the physical activities to a point where pain is not produced is the first step in the treatment A period of rest with complete relaxation and perhaps additional sleep is often advisable Phenobarbital gr ½ (30 mgm) three or four times a day or some other form of mild sedative often is helpful or even essential to the promotion of relaxation and the induction of adequate sleep If there are breathlessness or signs of cardiac failure digitalis is indicated but otherwise not The diet should be simple and overeating avoided Excessive

accumulation of gas may be a disturbing factor and perhaps associated with constipation Thus the function of the bowels should be controlled by as simple measures as possible in order to reduce the irritation to the minimum In the obese a gradual reduction in weight is indicated If the blood pressure in those with hypertension is not reduced sufficiently by rest relaxation and the reduction in weight of the obese the administration of nitrites is justified in order to reduce temporarily the work of the heart These preparations also have a favorable influence on the coronary circulation Nitroglycerin and amyl nitrite are commonly not employed except for the relief of pain However they may be used to advantage for the prevention of attacks When prescribed for this purpose one of these preparations preferably nitroglycerin should be taken a short time before the individual is obliged to undertake activities which may precipitate the pain A patient was seen recently who had been compelled to give up his work After a period at home he became irritable and despondent and the attacks occurred more frequently It was observed that following the administration of nitroglycerin gr 1/100 (0 6 mgm) he was able to walk a considerable distance without distress Accordingly he was advised to take the drug three or four times a day and engage in mild physical activities such as walking Thereafter he was free from attacks and the mental state was greatly improved With the more frequent use of nitroglycerin such as employed in the above patient one would expect greater effect on the coronary circulation The work of Schlesinger Blumgart and their associates[6, 19] have demonstrated conclusively that the development of collateral circulation is the most important means of postponing the inevitable effects on the heart from coronary artery disease This is accomplished for the most part by changes in the smaller arteries and the vasodilators act on vessels of this size

There are instances in which such factors as infection enlarged prostate diabetes anemia thyrotoxicosis hypothyroidism etc may be contributing to the development of the angina The various possibilities should be weighed carefully and judicious treatment employed Too rigid control of a mild diabetes however is not justified and when insulin is employed hypoglycemia should be avoided It is well established that the angina may be aggravated under these circumstances Moreover in hypothyroidism it is important that caution be exercised in the use of thyroid medication otherwise the increased demands on the heart imposed by the elevation of the metabolic rate may overweigh the beneficial effects from abolishing the hypothyroid state

The various theophylline and theobromine preparations have their

place in the treatment of angina pectoris because of their dilatory action on coronary vessels. Their possibilities are not great because of the extent of the coronary artery disease usually present. Nevertheless they should be given a chance in combination with various other measures and favorable results are observed not infrequently[30 31 32]. The writer has employed theophylline ethylenediamine for years and is convinced of its value. The usual dosage is gr 1½-3 (0 1-0 2 gm) 3 to 4 times a day. If beneficial effects are not obtained by the usual dosage it should be increased. Others favor the use of theobromine preparations such as the alkaloid theobromine gr 5 to 7½ (0 3-0 5 gm) theobromine calcium salicylate gr 7½ (0 5 gm) or theobromine sodium acetate gr 10 (0 6 gm) 3 times a day. All of these purine base derivatives may cause gastric irritation but in the experience of the writer this has not been an objectionable feature with theophylline ethylenediamine.

Nitroglycerine 1/100 grain (0 6 mgm) frequently gives prompt relief from an attack. It should be available always and taken at once with the onset of pain and repeated if necessary. Occasionally unpleasant and in rare instances ill effects are observed; therefore the drug should not be prescribed until its action is determined.

Surgical Treatment

In the more severe form it may be impossible to control the attacks by medical measures and so various surgical measures have been proposed. The first of these was concerned with the removal or section of different portions of the sympathetic chain. Favorable results were reported. However after it was demonstrated that paravertebral injections with alcohol served the same purpose in a more satisfactory manner and without subjecting the individual to a major operation the former was discontinued. Swetlow[33] in 1931 reported on the use of the latter treatment in 8 patients and stated that relief was obtained in every instance. J C White[34] since then has investigated carefully the possibilities of the procedure and in 1936 gave the detailed results of 37 injections. They were recorded as good (90 to 100 per cent relieved) in 70 3 per cent, as fair (50 to 90 per cent relieved) in 5 4 per cent and as failure in 8 1 per cent. In discussing the selection of cases it was pointed out that only those were accepted for injection who had not responded to medical treatment and who had continued to suffer so severely that the pain was unbearable. White regards this as the safest surgical method of treating angina pectoris and cites instances of remarkable recovery. It should be borne in mind however that this should not be

accumulation of gas may be a disturbing factor and perhaps associated with constipation Thus the function of the bowels should be controlled by as simple measures as possible in order to reduce the irritation to the minimum In the obese a gradual reduction in weight is indicated If the blood pressure in those with hypertension is not reduced sufficiently by rest relaxation and the reduction in weight of the obese the administration of nitrites is justified in order to reduce temporarily the work of the heart These preparations also have a favorable influence on the coronary circulation Nitroglycerin and amyl nitrite are commonly not employed except for the relief of pain However they may be used to advantage for the prevention of attacks When prescribed for this purpose one of these preparations preferably nitroglycerin should be taken a short time before the individual is obliged to undertake activities which may precipitate the pain A patient was seen recently who had been compelled to give up his work After a period at home he became irritable and despondent and the attacks occurred more frequently It was observed that following the administration of nitroglycerin gr 1/100 (0 6 mgm) he was able to walk a considerable distance without distress Accordingly he was advised to take the drug three or four times a day and engage in mild physical activities such as walking Thereafter he was free from attacks and the mental state was greatly improved With the more frequent use of nitroglycerin such as employed in the above patient one would expect greater effect on the coronary circulation The work of Schlesinger Blumgart and their associates[6, 19] have demonstrated conclusively that the development of collateral circulation is the most important means of postponing the inevitable effects on the heart from coronary artery disease This is accomplished for the most part by changes in the smaller arteries and the vasodilators act on vessels of this size

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attempted except by one who has expert anatomical knowledge of the structures concerned and experience *Total thyroidectomy was introduced* by Levine[35] and Blumgart[36] and their coworkers for the treatment of the more refractory cases on the basis that the resulting reduction in the basal metabolic rate might diminish the work of the heart sufficiently to permit the restoration of the cardiac function In the beginning the results apparently were very encouraging however, because of the magnitude of the procedure and the fact that various sequelae may develop it is seldom employed now More recently Beck[37] and others have attempted to improve the circulation of the heart by the production of extracardiac anastomosis The results so far are not particularly encouraging

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PART II

CORONARY THROMBOSIS (CARDIAC INFARCTION)

INTRODUCTION

The occlusion of one or more of the main branches is common in the advanced stages of coronary artery disease This may develop gradually from the progression of the arteriosclerotic process or occur rather abruptly from the formation of a thrombus at a site where the lumen of the vessel is narrowed In the gradual development conditions are favorable for the formation of collateral circulation and while there may be a deficiency of the blood supply to a section of the myocardium resulting in angina pectoris or perhaps later in cardiac failure the occlusion is not recognized during life In the abrupt development on the other hand the blood supply to an area of the cardiac muscle is reduced more or less suddenly restoration of this by collateral vessels usually is not possible consequently varying degrees of myocardial degeneration result and thus the heart commonly is affected or even seriously embarrassed at the time of or shortly following the thrombosis of the artery The occlusion associated with syphilitic aortitis as previously indicated in the discussion of angina pectoris generally is confined to the ostia of the coronary arteries and results from the extension of the syphilitic process Occasionally obstruction of one of the larger vessels is produced by embolus from subacute bacterial endocarditis or other sources In subacute bacterial endocarditis the smaller arteries commonly are occluded by emboli This is no doubt one of the important causes for the increase in the size of the heart and possibly the development of cardiac failure in this condition

OCCURRENCE

Coronary thrombosis is encountered occasionally in individuals before 40 years of age and is observed frequently between the ages of 40 and 50 years About 90 per cent however occur after 50 years of age Opinion is divided regarding the factors precipitating coronary thrombosis Some[1 2] have emphasized unusual physical strain emotional stress etc whereas others particularly Master and his associates[3] contend that it is not possible to correlate the onset of the attack with any preceding

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though both main branches of the left coronary artery and the main stem and the larger branch of the right coronary artery were occluded. This heart was that of a woman 60 years of age who had experienced dyspnea, palpitation and attacks of angina pectoris for two years before admission to the hospital. Total thyroidectomy was performed and she was free from symptoms for 19 months. Following this the angina returned and became increasingly severe. Death finally occurred from cardiac failure 34 months after the operation. It was concluded that the more recent thrombosis was responsible for the fatal termination despite the absence of infarct. The fact that there was practically no fibrosis of the myocardium is also of particular interest.

Jores[10] and others have pointed out that in arteriosclerosis of the coronary arteries the process involves mainly the larger and medium sized vessels and that the arterioles rarely are concerned. Saphir and his coworkers[8] found no relation between the gross lesions of the larger arteries and the histological changes in the smaller vessels, arterioles. They pointed out that often the latter showed no significant alterations even in the presence of pronounced disease of the larger arteries and that thickening of the arterioles was disclosed in only a few sections of the myocardium. Moreover in the arteriolar sclerosis of hypertension the arterioles usually are implicated to a minor extent as compared to that found in other organs[11]. This is of great importance for the smaller vessels serve a significant function in the development of collateral circulation.

The heart commonly presents varying degrees of hypertrophy and dilatation. However there is no relation between the extent of the cardiac enlargement and that of the disease of the coronary arteries. Thus it is generally known that the heart may be normal in size in the presence of extensive sclerosis of the coronary vessels. In 113 cases analysed by Nathanson[1], selected because they showed an advanced stage of the disease with marked narrowing or obstruction of one or more larger arteries, 45 (40 per cent) of the hearts weighed 400 grams or less. Furthermore in 12 of the 24 with occlusion of one of the main branches the weight did not exceed 400 grams. Palmer[13] studied the size of the heart roentgenologically in 200 patients who had survived coronary thrombosis by at least three months. About one third of the series failed to show or develop definite cardiac enlargement although observed over periods averaging more than three years following the coronary thrombosis despite the fact that several had had subsequent attacks. Hypertension is regarded generally as being the most important cause of the cardiac enlargement that precedes the onset of cardiac failure.

event However the presence of capillaries in the intima of coronary vessels presenting advanced arteriosclerosis especially in the vicinity of atheromatous plaques and the fact that hemorrhage into the intima presumably from the rupture of these capillaries is commonly associated with the development of a thrombus[4] [5] seem to be highly significant It would appear that any undue strain on the coronary vessels under these circumstances might well bring about the rupture of capillaries resulting in hemorrhage and thus precipitate the formation of thrombus Complete obstruction of the vessel by the thrombus as pointed out by Paterson[4] may not occur for hours or even days following the hemorrhage into the intima and the possible precipitating factor be overlooked There are quite likely other factors that contribute to the development of coronary thrombosis Leary[6] has demonstrated that the rupture of an atheromatous abscess may result in the formation of a thrombus The occurrence of coronary thrombosis during shock incident to trauma and surgical operation has been attributed to a further reduction in the rate of blood flow through a narrowed lumen because of fall in blood pressure[7]

Pathology

The coronary arteries usually present extensive arteriosclerotic changes While ordinarily this is more advanced in one vessel particularly the anterior descending branch of the left coronary artery it generally involves to a varying extent the right coronary artery the circumflex branch of the left coronary artery and their main branches This feature was emphasized by the observation of Saphir Priest Hamburger and Katz[8] Both coronary arteries were involved in each of the 34 hearts examined In those with myocardial infarct at least two branches supplying this particular area were diseased There were two instances in which a recent thrombus was found in one vessel and a resulting infarct was located in the area supplied by an adjacent artery which had been occluded previously This situation was explained on the basis of the development of collateral circulation An infarct was observed in four instances in the absence of occlusion However it was noted that the lumen of the arteries concerned was greatly reduced The results of the comprehensive studies by Schlesinger[9] and by Blumgart Schlesinger and Davis[7] are in accord with the above observations Of the 30 cases recorded by Blumgart Schlesinger and Davis[7] 19 showed complete obstruction of two or more larger vessels In one instance cited by Schlesinger there was satisfactory injection throughout the heart even

the basis of these experiments they concluded that in man if the duration and degree of the disproportion between the supply of blood and the demands of the heart are sufficiently great infarction of the myocardium occurs and that this does not necessarily depend on the presence of a thrombus

In cardiac infarction the destructive process often extends to the endocardium and mural thrombi commonly develop Blumer[15] on the basis of personal observation and the review of the literature estimates that this occurs in about 50 per cent of the cases The mural thrombi may be limited to the left ventricular cavity but are frequently present in both the right and left sides of the heart According to the figure presented by Blumer embolic manifestations occur in about 14 per cent of the cases and are more likely to take place during the first 10 days following the coronary thrombosis The lungs brain, extremities and kidneys were involved in the order mentioned

With more extensive necrosis the left ventricular wall occasionally ruptures permitting hemorrhage into the pericardial sac and resulting in death This usually involves either the anterior or posterior wall In rare instances it concerns the interventricular septum or papillary muscle There are other cases in which the destructive process is so wide spread that a section of the wall of the left ventricle is largely replaced by fibrous tissue This may ultimately permit bulging of the ventricular wall forming aneurysm The more common location is the anterior apical region, and the lesion under these circumstances results from the thrombosis of the anterior descending branch of the left coronary artery

It is apparent from the foregoing discussion that the heart may withstand repeated major insults to the coronary circulation without gross and perhaps microscopic changes in the myocardium In fact the disease of the coronary arteries is the only constant feature This can be explained only on the basis of the development of collateral or accessory circulation The experimental ligation of one of the main branches of the coronary arteries always produces an area of infarction[16] It is quite possible that under similar circumstances the same would obtain in man Thus with a normal coronary circulation it would seem that if the blood supply to a large area of the myocardium is interrupted suddenly it is not possible for this to be restored completely by adjacent vessels The fact that there is rather striking variation in the size of the resulting lesion when the same vessel is ligated at corresponding levels indicates that at least in certain instances there is considerable collateral circulation Anastomosis between adjacent vessels no doubt varies in extent

Thrombosis of one of the larger branches usually results in an area of infarction which if the subject survives is replaced ultimately in part by fibrous tissue The most characteristic lesion of this type generally results from the thrombosis of the anterior descending branch of the left coronary artery This involves the anterior apical wall of the left ventricle the lower anterior section of the interventricular septum and to a varying extent the adjoining anterior wall of the right ventricle Infarcts are observed frequently on the posterior and occasionally on the lateral wall of the left ventricle They are encountered seldom in the right ventricle except when associated with involvement of the adjacent section of the left ventricle Occlusion and thrombosis of the right coronary artery are common However if an infarct results it usually is located in the area supplied by the posterior descending branches Since these branches commonly pass across the interventricular septum to the left ventricle the site of the lesion usually is in the latter location Thrombosis of the circumflex branch of the left coronary artery may result in infarct involving the lateral or posterior wall of the left ventricle depending on the extent to which this vessel contributed to the blood supply of the latter area The lesions involving the lateral or the posterior wall of the left ventricle usually are not so sharply defined as that on the anterior surface resulting from the closure of a descending branch of the left coronary artery

There is a remarkable variation in the extent of the myocardial damage following the obstruction of the main branches of the coronary arteries Oberhelman and LeCount[14] pointed out that there may be no gross or microscopic changes in the cardiac musculature following the closure of either the right or left coronary artery and also cite the observations of Calli and Merkle The case previously cited from the study by Schlesinger is a striking example It is to be recalled that in this instance there was very little fibrosis of the myocardium despite the fact that both branches of the left coronary artery and the main stem and the larger branch of the right coronary artery were completely obstructed While a recent thrombus was responsible for one of the occlusions this did not result in the development of an infarct The closure of a vessel by thrombus without the production of degenerative changes in the myocardium is not an unusual circumstance On the other hand an infarct is encountered occasionally in the absence of coronary thrombosis This condition was observed four times by Saphir and his coworkers[8] and twice by Blumgart Schlesinger and Davis[7] Blumgart and his associates have shown that if the main coronary artery of the dog is occluded for longer than 20 minutes degenerative changes occur in the muscle On

In the normal subject the communications between adjacent vessels are limited and in most instances take place by means of smaller vessels There fore the abrupt closure of one of the main branches early in the course of the disease usually results in a large area of infarction If on the other hand the obstructive process develops slowly and is not terminated too soon by thrombus there may be very little or perhaps no significant degeneration of the myocardium Thus the rate of the formation of the obstruction determines in a large measure the extent of the collateral circulation the histological changes in the myocardium the efficiency of the heart and perhaps the character of the clinical manifestations

Symptoms

Severe and lasting pain and intense dyspnea coming on suddenly and unexpectedly are the most outstanding and characteristic symptoms of coronary thrombosis Either of these particularly pain may be present without the other but commonly they are associated to a varying extent They are indicative of a prolonged or permanent insufficiency of the circulation to a section of the myocardium and the latter commonly is referred to as acute left ventricular failure Of these pain is far more often the predominant symptom and its significance is recognized more generally In the typical case the distribution character and duration the accompanying shock the fall in blood pressure the signs of cardiac damage and the later development of fever and leucocytosis produce a distinctive clinical picture that is well known When the onset is with paroxysmal dyspnea usually there is obvious evidence of acute structural alterations in the heart Between these types of onset there is a wide range in the clinical expression Thus the effects on the heart may be so overwhelming that the patient dies suddenly or so slight that few or no symptoms are produced and the condition is not recognized Again in the instances in which pain and shock predominate the clinical picture the associated symptoms and the signs of cardiac damage may vary to a remarkable extent In some there may be no apparent dyspnea and perhaps no definite evidence of structural changes in the heart except as demonstrated by the electrocardiogram

Many give a history of previous attacks of chest pain typical of angina pectoris and in another group the coronary thrombosis is the first evidence of coronary artery disease The onset of the pain usually is quite abrupt but occasionally gradual extending over a period of several hours or perhaps even two or three days as illustrated by the following patient

probably effective for the most part through the smaller branches or perhaps may exist in potential state until there is need for it Wiggers[17] concluded that the communication between normal vessels is extremely small but further states that this does not preclude the enlargement of minute potential channels nor the development of new ones when a main branch is occluded slowly This would seem to underestimate the possibilities particularly in view of the investigation of Blum Schauer and Calef[18] These observers studied the effects of gradual occlusion of the anterior descending branch of the left coronary artery in 14 dogs over periods averaging five weeks in duration In 10 of these animals there was no gross evidence of an infarct and moreover in 4 there was no histological change in the myocardium

It is well known that commonly there is free communication between vessels in which one has been gradually obstructed The need for this is obvious and has been emphasized repeatedly This question has been investigated more recently by Schlesinger[7 9] using an improved method consisting of a combination of multicolored radiopaque injection material and complete dissection In a group of 35 hearts taken from subjects over 55 years of age extensive collateral circulation was disclosed in only those instances in which there was occlusion of the coronary arteries Anastomosis however was demonstrated in 5 hearts none of which showed more than a few scattered atheromatous plaques The importance of an obstructive process was especially stressed but it is apparent that this is not necessarily always present Wearn and his associates[19] and others have shown that under adverse circumstances the Thebesian veins may contribute to the blood supply of the myocardium Finally Beck and Tichy[0] and Robertson[1] have demonstrated the importance of extracardiac circulation In the investigation by Robertson the coronary sinus the main veins and the coronary arteries were ligated successively and finally in certain instances the pericardial adhesions later were separated In a typical protocol cited the first procedure was carried out on February 20th and the final the sixth on August 18th In the last operation the pericardium was stripped from the myocardium The dog died in October from cardiac failure These operations resulted in the development of extensive communications between the heart and extracardiac vessels which were regarded as being mainly responsible for the maintenance of the cardiac circulation

In conclusion it may be said that the response of the heart in any particular instance no doubt is influenced by many factors but the ability to maintain an adequate circulation to the myocardium through the development of collateral circulation is perhaps the most important

pulse however may continue for days depending on the extent of the impairment in the cardiac function The systolic blood pressure may recede to 90 or lower In those with previously unrecognized hypertension the extent of the reduction in blood pressure usually is not appreciated The blood pressure ordinarily rises slowly but often remains at a level considerably below the original Following the occlusion of the smaller vessels there may be no change in the blood pressure or if so perhaps only slight and transient in nature With pronounced reduction in blood there may be suppression of the urine and occasionally nitrogen retention develop

In the past it has been assumed generally that sudden death the unexpected occurrence of acute left ventricular failure or the appearance of severe and persistent anginal pain accompanied by shock and the associated fall in blood pressure in an individual with coronary artery disease was due to coronary thrombosis More recently however it has been shown that these are not necessarily precipitated by the closure of a vessel Levy and Bruenn[**] reported a series of 25 cases of sudden death in which recent coronary thrombosis was not disclosed at necropsy and attributed the fatal termination to acute insufficiency of the coronary circulation They also concluded that attacks of non fatal character such as mentioned above may occur likewise in the absence of coronary thrombosis These observations have been verified and extended by others particularly by Blumgart Schlesinger and Davis[7] Thus clinical manifestations that heretofore have been explained on the basis of the closure of a coronary artery may be induced in an individual with impaired coronary circulation by factors which impose excessive demands on the heart If the insufficiency of the coronary circulation and the resulting anoxemia are transient and pain occurs the attack is diagnosed as angina pectoris If on the other hand the disproportion between the blood supply to the myocardium and the requirements of the heart is more advanced and sufficiently prolonged more profound symptoms occur certain of the muscle fibers may not survive or even infarct result With the development of an infarct the clinical manifestations resulting from the insufficiency of the coronary circulation usually are supplemented by the appearance of persistent changes in the electrocardiogram fever leucocytosis increase in sedimentation rate and perhaps pericardial friction rub

PHYSICAL FINDINGS

There is necessarily a great variation in the physical findings In many there has been hypertension with the customary changes in the

A man 60 years of age had a feeling of constriction in his chest while showing a friend about his place of business This was not severe and lasted only a few minutes The following day he had the same discomfort under similar circumstances Thirty six hours later he was awakened at 12 30 in the morning by intense pain in his chest which lasted about one and one half hours When seen two days later there was unmistakable evidence of acute myocardial damage

The patient frequently is awakened from sound sleep during the night and often during the early hours of the morning by terrific distress The site of the pain is similar to that of angina pectoris except for a greater tendency to an involvement of the lower sternum and the upper abdomen In rare instances as in angina the distress may be entirely confined to the abdomen With the latter location in particular not infrequently there is nausea and vomiting or even diarrhea Furthermore the pain usually has a greater area of distribution than that of angina pectoris Whereas in those with a previous history of the latter the pain may have extended to the left arm with the development of coronary thrombosis frequently it is felt in both arms and possibly over greater areas of the chest In the mild form and in those with gradual onset the distress is described often as a feeling of oppression or heaviness in the chest On the other hand it may be the most agonizing tearing boring or constricting pain The duration in the more severe form varies from a few hours to days and may persist to a minor extent even after repeated hypodermic administrations of morphine It is ordinarily not influenced to any significant extent by nitroglycerin While the above type of pain often follows the thrombosis of a larger vessel instances of fairly extensive infarction are encountered not infrequently at necropsy which were not manifested by significant symptoms The pain if present must have been of a very mild nature or in cases with angina pectoris perhaps no more than that ordinarily experienced

The extent of the dyspnea is determined by the general effect on the cardiac function In some as previously indicated acute left ventricular failure is precipitated Thus pain and dyspnea are not necessarily present to the same extent Even with severe pain there may be no appreciable dyspnea In certain of these however cardiac failure may develop within a few days more particularly in those permitted to be up and about soon after the cardiac accident

The onset with severe pain or intense dyspnea ordinarily is accompanied by profound shock in which the ashen gray color profuse perspiration feeble pulse and fall in blood pressure are conspicuous features The normal color usually returns and the perspiration disappears after the pain or dyspnea subsides The exhaustion and feeble and rapid

extensive cardiac damage or a complication such as pulmonary infarction has occurred

The sedimentation rate produces another means of following the course of cardiac infarction It is usually increased by the second or third day to a level of 50 to 100 mm and remains elevated for some time after the fever and leucocytosis have subsided Some feel that it may be of value in estimating the rate of healing of the infarction Complications such as pulmonary embolus or infection regardless of the source likewise may elevate the sedimentation rate

Electrocardiographic Alterations

Electrocardiograms taken within a few hours or a few days following coronary thrombosis usually show displacement of the R–T and S–T segment The former arises from the R wave at varying levels above the iso electric line and the latter at approximately the same distance below the base line The character of this deviation varies It might be relatively flat or round or form a summit The amplitude usually is greatest in curves with prominent Q R S deflection As a rule the change is most conspicuous in leads I and III and generally assumes the opposite direction in these leads Usually it is noted during the first week but might persist for several weeks In time this is replaced by a T wave which assumes a direction opposite to that of the former Thus the displacement of the R–T segment is followed by the development of a negative T deflection and that of the S–T segment by an upright T wave This results in two general forms of curves which are designated as T_1 and T_3 types In the T_1 type electrocardiogram this wave is sharply negative in lead I possibly slightly so in lead II and upright in lead III and perhaps to a slight extent in lead II whereas in the T_3 type the order is reversed with a positive deflection in lead I and a negative phase in lead III These waves are usually identical in leads I and III except for the direction assumed The T_1 type of curve usually is associated with an infarct located in the anterior apical wall of the left ventricle and the T_3 type with a lesion involving the posterior wall of the left ventricle This apparently holds only for the cases in which there is a single infarct in either the anterior or posterior wall of the left ventricle When there are independent coexisting lesions one in the anterior wall and the other in the posterior wall the electrocardiogram might be either of the T_1 or T_3 type The kind of curve obtained under these circumstances apparently is determined by the lesion of more recent origin It should be borne in mind however that even with a single lesion it is not always

cardiovascular system Again, the results from physical examination prior to the accident may be surprisingly negative During and even after a severe attack of pain not infrequently there is very little appreciable alteration in the heart The cardiac rate usually is accelerated but seldom is above 100 per minute In rare instances it may be reduced from the development of heart block Premature beats are noted often and occasionally ventricular tachycardia appears likewise auricular fibrillation or auricular flutter Of these auricular fibrillation is more common but usually occurs in paroxysms Alteration in the character of the cardiac tones resulting in poor differentiation is one of the earliest and most constant findings When accompanied by gallop rhythm this constitutes unmistakable evidence of cardiac damage A systolic murmur may be heard at the apex or occur later from the dilatation of the mitral ring or because of involvement of the papillary muscles It is often faint in the beginning but may become more prominent later There may be no appreciable increase in the size of the heart When dyspnea is a conspicuous feature however there is usually obvious evidence of cardiac damage with signs of pulmonary congestion or even perhaps pulmonary edema With thrombosis of the right coronary artery right heart failure manifested by the appearance of distention of the veins engorgement of the liver and peripheral edema may occur Jaundice is observed occasionally

The extension of the infarct to the epicardium commonly results in the development of a pericardial friction rub This is often faint and thus readily overlooked It usually appears on the second to the fourth day generally is heard between the apex and the sternum occasionally at a higher level and ordinarily subsides after one or two days It is one of the more distinctive signs of cardiac infarction and therefore highly significant in doubtful cases

The temperature and leucocyte count is of considerable importance in establishing the diagnosis and following the course of coronary thrombosis The extent to which these are elevated apparently is dependent on the amount of myocardial damage Fever ranging from 99° to 10_° F usually is not noted until the following day and ordinarily reaches the highest peak on the third or fourth day after which usually it subsides In an occasional instance however it may persist for a week or longer An increase in the leucocyte count has been observed as early as one or two hours after the onset of clinical manifestations of coronary artery disease This in general parallels the temperature and ranges from twelve to twenty thousand per cubic millimeter If the temperature persists and the leucocyte count remains elevated it is certain that

Heart Association and the Cardiac Society of Great Britain and Ireland to study the problem These committees jointly recommended that when a single precordial lead is used lead IV F be given the preference To take this lead the left leg wire is connected to the precordial electrode and the left arm wire to the left leg and the lead switch is turned to lead III The precordial electrode is placed on the extreme outer border of the apex beat as determined by palpation If it is not possible to locate the apex beat by palpation the electrode is placed in the fifth interspace just outside of the left border of cardiac dullness

In normal subjects lead IV F presents an upright P diphasic Q R S and positive T wave When the lesion involves the anterior wall of the left ventricle the Q R S usually becomes monophasic and negative and the S–T segment is elevated Later the upper displacement of the S–T segment is replaced by a sharp negative T deflection The changes usually are not so evident when the infarct involves the posterior wall of the heart Under these circumstances there is commonly a prolongation or depression of the S–T segment This is followed frequently by the development of an increase in the height of the T wave

It is evident from the foregoing discussion that the entire ventricular portion of the electrocardiogram may be modified Certain of the more important changes are closely related and undergo a distinctive evolution In the beginning the displacement of the R S–T segment commonly is the most conspicuous feature This however may not appear or if present usually disappears within a few days The deviation in the R S–T segment is replaced by alterations in the T wave the direction of which is opposite to that of the former The T wave usually presents a sharp peak and is constantly undergoing changes until its stationary stage is reached This is more apparent during the first few days or weeks following the obstruction of the coronary vessel The above changes not infrequently are accompanied by the appearance of a prominent Q wave reduction in amplitude or perhaps a bizarre form of Q R S deflections With the latter there may be an increase in the duration of the Q R S group and occasional bundle branch block is observed

The electrocardiogram frequently affords the only means of demonstrating acute myocardial damage Distinctive alterations usually are evident in the standard leads if a record is obtained early and thereafter at one to two days intervals during the first week or ten days These changes however are generally more apparent when a precordial lead is employed It should be borne in mind also that there is remarkable variation in the characteristics and magnitude of the various alterations In the first place the displacement of the R S–T segment may be absent

possible to localize it by the character of the electrocardiogram More over electrocardiograms that do not conform to either T_1 or T_3 types occur

The subsequent alteration in the T wave is one of the more distinctive features in the electrocardiographic changes associated with coronary thrombosis There is a tendency for this deflection to return to the original form The time required varies from a few days to weeks or months In some the normal is restored but in many the T deflection remains permanently negative in one or more leads

Within recent years attention has been directed to the appearance of a prominent Q wave which has been attributed to a lesion involving the interventricular septum Wilson and his associates have observed that in T_1 type of curves there is often a conspicuous Q wave in lead I This is associated generally with a greatly reduced amplitude of the other deflections of the Q R S group With this there is frequently a prominent S wave in leads II and III It was further pointed out that a Q wave in lead I may be very large and the S wave in leads II and III small or absent The T_3 type of curve often is accompanied by a large Q wave in leads III and II The Q wave in general is more persistent than the alterations in the R S–T segment and the T wave and it has been suggested that it should direct attention to the possibility of coronary thrombosis after the other signs have disappeared or have lost their characteristic features

Alterations of less significant character frequently occur The various types of irregularities have been mentioned Of these premature contractions generally of ventricular origin are the most common and occasionally ventricular tachycardia develops Auricular fibrillation and auricular flutter likewise may appear and not infrequently in paroxysms Bundle branch block and intraventricular conduction defects of varying degree giving rise to a great variety of alterations in the ventricular complexes such as slurring and splintering of a chief ventricular deflection with an associated increase in the duration of the Q R S group are observed fairly commonly The occurrence of bundle branch block may mask the changes usually noted in the T wave and the R and S–T segments Finally in certain instances there is a conspicuous reduction in the amplitude of the more prominent ventricular deflections which may be transient or permanent

These changes commonly are more evident in the fourth lead Within recent years various precordial leads have been employed however the variations in the technic and nomenclature led to confusion In order to clarify the situation committees were appointed by the American

Diagnosis

The diagnosis usually is apparent from the history alone in a typical case Because of the wide range in the clinical expression however the condition commonly is overlooked or confused with other disorders In the first place coronary thrombosis not infrequently is relatively silent and thus perhaps not suspected during life Furthermore in the cases in which pain is the outstanding feature there is a remarkable variation in the severity and distribution This is generally responsible for the errors in diagnosis For one thing the profession has been greatly impressed by the intensity of the pain commonly associated with the condition and consequently the possibility of a cardiac accident is foremost in the mind when distress of this general character appears in the chest from other causes such as syphilitic aortitis dissecting aneurysm rupture of the aorta pulmonary embolism acute pneumothorax and possibly massive collapse of the lung Moreover the fact that the pain may be no more severe than that experienced with angina pectoris still is not generally appreciated As previously pointed out attacks of this character not infrequently precede the onset of more severe symptoms by hours or even days In the differentiation between angina pectoris and coronary thrombosis the circumstances under which the pain occurs always should be taken into consideration Pain of this character is more significant when it occurs for the first time while the subject is at rest Furthermore in those with angina of effort attacks more severe than usual and particularly when they appear while the individual is at rest may be on the basis of coronary thrombosis as illustrated by the following patient

This man was admitted recently to the hospital because of bladder obstruction from hypertrophy of the prostate He gave a history of having had angina of effort for eight years but during the past year the attacks had been much less frequent and of a rather mild character Following admission to the hospital however there were a few days during which he experienced frequent attacks while in bed It is possible that bladder spasms may have been a contributing factor However conspicuous and persistent alterations occurred in the electrocardiogram which were regarded as being indicative of acute myocardial damage

In this connection it is well to bear in mind that coronary thrombosis not infrequently develops following an operation or for that matter any condition which requires bed rest Of 625 cases of coronary thrombosis observed by Master Dack and Jaffe [7] 35 occurred following operations Moreover there were 13 additional cases in which the condition was suspected but not included because of the lack of necropsy or electro

Thus the more important abnormalities may concern the T wave and these may escape detection unless serial curves are taken during the early stages of the condition The magnitude of the alterations is determined largely by that of the Q R S group and is ordinarily greatly reduced if the amplitude of the latter is low Thus in any given case there may be various modifications in the electrocardiogram but the consecutive changes are the most important There are many instances in which the modifications in the electrocardiogram are of such character that there can be little doubt regarding their significance The evidence obtained from this method of examination however always should be weighed carefully with that elicited by other means Moreover, the alterations in the electrocardiogram rarely justify a statement regarding the prognosis (For other discussion of the electrocardiogram in coronary thrombosis with illustrative electrocardiograms see Vol II Chapt XI Part II)

Roentgenological Examination

Shortly following the ligation of a coronary artery the area of the heart wall supplied by this vessel ceases to contract and moves in the opposite direction to that of the surrounding cardiac musculature[5] This establishes a basis for the use of the kymograph and the fluoroscope in the diagnosis of cardiac infarct Various types of abnormalities are observed in the area of infarction These usually consist of reversal partial reversal or absence of movement[6] Occasionally however there are multiple small bizarre movements or perhaps double systolic pulsations In a series of 45 cases of coronary thrombosis studied by Gubner and Crawford[6] employing the kymograph evidence of the presence of an infarct was recorded in 41 The location of the lesion corresponded with that indicated by the electrocardiogram in 25 In 6 instances the information derived from the kymographic study pointed to the presence of a lesion both in the anterior and posterior wall of the left ventricle whereas that from the electrocardiogram suggested that the infarct was located in one or the other In general the localization by means of the kymograph was more accurate when the lesion involved the anterior wall It was interesting to note that in 6 patients with coronary artery disease but without definite evidence of coronary thrombosis the alterations in the kymogram were very suggestive of the presence of an infarct With care the abnormalities in the movements resulting from an infarct may be detected by the fluoroscope The roentgenogram does not ordinarily give information concerning the presence of an infarct unless there is a rather conspicuous bulging (aneurysm) of the wall of the left ventricle

of morphine were required for relief The attending physician thought that the patient had gall bladder disease but there was never any pain in the abdomen and moreover he was not able to elicit tenderness in the region of the gall bladder Later jaundice appeared and was intense when the patient was admitted to the hospital There was no demonstrable evidence of coronary thrombosis This case later came to necropsy The gall bladder was filled with stones and several had passed into the common duct

Finally peptic ulcer gall bladder disease or pancreatitis is not infrequently associated with coronary artery disease

A heavy man 58 years of age had had occasional heartburn and belching of gas off and on for 25 years Three weeks before the writer saw him he contracted an upper respiratory infection and was advised by his family physician to force fluid Two days later after having taken large quantities of water and fruit juices he experienced a tight bursting like pain in the epigastrium lasting about 30 minutes The pain was so severe he stated that it affected his breathing Attacks of varying intensity continued to recur until after admission to the hospital Upon examination it was discovered that there was slight icteric discoloration of the sclerae The van den Bergh test made on the following day showed the bilirubin level of the blood to be 3 1 mgm per cent The results from the physical examination of the heart were negative except for distant and poorly differentiated cardiac tones The blood pressure was 140 systolic and 100 diastolic mm Hg There was tenderness in the epigastrium and right upper quadrant of the abdomen but no mass was felt The gall bladder was not visualized in the roentgenological examination Certain of the stools were quite bulky and chemical examination disclosed the fat content to be increased and the enzymes reduced Six electrocardiograms were taken during a period of ten days and rather striking alterations were observed In the first curve the T wave was sharply negative in lead I and showed a prominently upright deflection in lead III whereas in the last one taken the situation was reversed in that the T wave was now a positive phase in lead I and negative in lead III

The build of this patient the history of indigestion the presence of jaundice the results of the roentgenological examination of the gall bladder and the findings from the chemical determination of the fat and enzyme content of the stools pointed to the possibility of gall bladder disease with perhaps pancreatitis The changes in the electrocardiogram on the other hand were highly suggestive of myocardial damage Another man 57 years of age in the hospital at the same time presented duodenal ulcer and coronary thrombosis

There are other features which may lead one astray in the diagnosis In certain instances the onset is with dizziness or with faintness which under rare circumstances may progress to coma Auricular fibrillation auricular flutter or ventricular tachycardia may be an early feature Oc

cardiographic confirmation In the proven cases pain usually was absent or slight the symptoms more often being dyspnea cyanosis and shock

Finally as previously pointed out there are cases in which there is little or no pain In certain of these the initial manifestation is that of paroxysmal dyspnea (acute left ventricular failure) The incidence of this type of onset is probably much greater than is appreciated generally The rapid development of cardiac failure in a subject of arteriosclerotic age should direct attention always to the possibility of a coronary accident

Atypical distribution of pain particularly the involvement of the epigastrium often is responsible for diagnostic difficulties Occasionally the distress is limited to this region as in the following case

A man 50 years of age was admitted to the hospital because of dyspnea cough and fever He was so ill at the time that it was not possible to obtain a satisfactory history Because of the presence of fine moist rales in the base of the right lung and blood tinged sputum a tentative diagnosis of pneumonia was made This was also the roentgenological diagnosis from a film taken of the chest the following morning by a portable machine It was apparent from the first examination that there was cardiac damage Moreover the electrocardiogram showed prominent alterations These changed from day to day and were of the character usually observed in coronary thrombosis In addition to this there was a very definite progression of the cardiac disability during the first thirty six hours in the hospital as manifested by periods of intense dyspnea the appearance of gallop rhythm premature beats and finally paroxysms of auricular fibrillation After the patient had recovered to a point when a reliable history might be obtained it was found that he was suddenly taken ill about ten o clock in the evening a few days prior to admission to the hospital following a heavy meal of steak and onions with intense pain in the epigastrium accompanied by nausea After about one and one half hours he vomited profusely and had a copious watery bowel movement following which the pain disappeared

The diagnosis is further complicated by the fact that in conditions of the upper abdomen such as perforating peptic ulcer acute pancreatitis and particularly gall bladder disease the pain may extend to the chest This feature was especially impressed on the writer by a patient studied in 1931

A man 75 years of age had had for many years recurring attacks of indigestion consisting of a feeling of fullness in the epigastrium accompanied by consciousness of gas Five weeks before coming to the hospital he was awakened at two o clock in the morning by severe pain across the anterior chest extending from the middle of the sternum to the episternal notch and laterally to the anterior axillary line on each side The pain persisted for several days and many hypodermic injections

ing to note that in the cases that came to necropsy there was in most instances an old thrombosis in addition to the recent one The fact that two thirds of these cases had cardiac failure would indicate that either the heart was already badly damaged or that there was an extensive infarction with the more recent attack It is well recognized that the mortality from the second attack always is greater than that from the first The results from a study such as carried out by Master and his associates obviously will vary with the material available Ordinarily only those with extensive cardiac damage are sent to the hospital Certainly the incidence of cardiac failure recorded above is far greater than that observed by the writer

Despite a favorable condition at the onset the subsequent course is always in doubt Thus there is always the possibility of the extension of the infarct the development of a new one embolic manifestations or perhaps the rupture of the wall of the left ventricle These various complications were discussed in connection with the pathology of coronary artery disease under the heading Pathology

The experience of more recent years has greatly modified the concept of the outlook of coronary thrombosis Thus instances of recovery are common in every large series of coronary artery disease In a series of 286 cases reported by Conner and Holt [9] the immediate mortality was 16 2 per cent Of the 117 patients who recovered satisfactorily from the first attack 75 per cent were in good health at the end of two years 21 per cent at the end of five years and 3 4 per cent at the end of ten years Of 200 cases analyzed by Bland and White[30] 101 were known to be dead and 91 alive The average duration of life following the attack was 1 5 years in the former and 3 2 years in the latter It is quite probable that certain of those of the latter may live for many more years

Recurring attacks are common as indicated by our own series and by that of Conner and Holt In our series it was estimated that 74 per cent had one attack and 25 per cent two or more In that analyzed by Conner and Holt 69 (24 per cent) had two attacks twelve (4 per cent) three attacks and fourteen (5 per cent) more than three attacks Of the 370 cases recorded by Willius[31] 297 (80 per cent) had a single attack and 63 (17 per cent) two attacks The average interval between attacks was 2 2 years with the shortest period being 12 hours and the longest 15½ years Eight patients had three attacks with an average interval of 3 9 years between the second and third There were two patients that had four attacks

In general the course is more favorable in those in whom the heart withstands the accident without signs of failure On the other hand the

casionally embolic phenomena are the first intimations of coronary accident

A careful detailed history taking into consideration age sex and all circumstances leading up to the episode under consideration is unquestionably the best safeguard against overlooking coronary thrombosis or mistaking it for some other condition In the writer's experience the failure to obtain some important bit of information from the history usually has been responsible for the error in diagnosis In the doubtful cases one should bear in mind the various possibilities but not come to a final conclusion until there is sufficient data to justify it Oftentimes the final decision in cases of coronary thrombosis is dependent upon the demonstration of acute changes in the myocardium Of the various physical signs the alteration in the cardiac tones resulting in a reduction in intensity and poor differentiation is the most common and the first to appear However one should not place too much reliance on this alone but be on the alert for further developments such as gallop rhythm premature beats and other forms of arrhythmia pericardial rub systolic apical murmur and perhaps the extension of the area of cardiac dullness The electrocardiogram not infrequently provides the only means of detecting cardiac damage and thus may establish the diagnosis It is extremely important however that a curve be taken early and at one or two day intervals

Course and Prognosis

The response of the heart depends on several factors such as the previous state of the coronary circulation size of the vessel concerned and the extent to which obstruction develops before the thrombosis occurs If as previously pointed out time is allowed for the development of collateral circulation there perhaps may be very little cardiac damage This accounts for the fact that many withstand the thrombosis of one of the larger vessels without any particular embarrassment of the heart In others there is obvious impairment in the cardiac function and in certain of these the heart is hopelessly crippled Finally there are those in whom the effect is so overwhelming that sudden death or extreme cardiac failure results In 140 consecutive cases analyzed by Master Dack and Jaffe[3] two thirds presented cardiac failure Of these 18 per cent had left ventricular failure alone and 48 per cent right and left combined There was a mortality of 30 per cent among those with cardiac failure and only 4 per cent in the remaining The average age of the group with heart failure was 57 years and that of the remaining 49 years It was interest

barrassment as evidenced by dyspnea and cyanosis When rapid action is desired a preparation for intravenous use may be added to the theophylline ethylenediamine and dextrose solution Thereafter it may be given orally either in the form of the powdered leaf gr 1½ (0 1 gm) or tincture minims 15 (1 cc) three or four times a day Large amounts are rarely necessary or advisable Cardiac failure not infrequently follows the temporary recovery from coronary thrombosis and oftentimes it is possible to restore the function by relaxation and sleep and the administration of digitalis Auricular fibrillation often is abolished by quinidine If however with auricular fibrillation there is evidence of cardiac failure digitalis is indicated and should be given in sufficient amounts to control the rate Fortunately however as previously indicated the auricular fibrillation seldom persists

The use of quinidine sulphate has been recommended as a precaution against the possible development of ventricular fibrillation or ventricular tachycardia While there may be some question regarding the routine administration of the drug it is unquestionably advisable in the presence of frequent premature beats particularly of ventricular origin

It is highly important that the patient be spared all unnecessary physical effort during the first ten days or two weeks Thus the bowel should be regulated by measures that will not produce frequent movements or entail undue strain in passing the stool The diet should be simple and of a character not calculated to promote abdominal distention

The duration of bed rest is determined by the circumstances A period of four to six weeks ordinarily is advised It is very questionable that less than four weeks is justified and there are many for whom a longer period may be necessary for the maximum restoration of the cardiac function This feature of the treatment therefore is largely a matter of judgment taking into consideration the extent of the myocardial damage Mallory Salcedo Salgar and White[37] have studied recently the rate of healing of myocardial infarction in 72 autopsied cases It was pointed out that necrosis of muscle and infiltration by polymorphonuclear leukocytes are the important features of the first week Connective tissue formation begins at about the second week These observers concluded that small infarcts are healed almost completely after a period of five weeks but larger lesions may require two months

The management of the patient after he is allowed out of bed is of the utmost importance It is essential that the physical activities be regulated carefully and not extended to the point where there is shortness of breath or pain Thereafter it is a matter of regulating the habits of living so that the individual may as far as possible stay within the limits

outlook is grave in the presence of extensive impairment of the cardiac function during the early course of the condition There are numerous exceptions however as indicated by the study by Conner and Holt Thus in the 102 cases in which they were able to study the relationship of the severity of the symptoms to the immediate prognosis almost one third of those that recovered were in the group with extreme initial manifestations In the patient previously cited, in whom the onset was with pain entirely confined to the epigastrium associated with nausea vomiting and diarrhea and the subsequent course that of profound left ventricular failure a very satisfactory cardiac function was established later Finally the course is dependent to a remarkable extent on the treatment immediately following the cardiac accident Even though the damage to the heart may not seem great at the time the chances for recovery may be eliminated by an inadequate period of absolute rest Moreover as in the case mentioned above it may be possible to bring about a most remarkable restoration of the cardiac function

TREATMENT

The outcome in coronary thrombosis is always in doubt The patient therefore should be confined to bed at as nearly absolute rest as possible and maintained in this state until the period of emergency has passed Protection of the heart at this time may not only determine the immediate outcome but have a deciding influence on the subsequent course Morphine is the most valuable remedy during this period of treatment and should be administered in sufficient amounts to control the pain and induce sleep After the pain has disappeared unless there is dyspnea a simple sedative such as phenobarbital usually is effective in promoting relaxation and sleep Oxygen is indicated in the presence of dyspnea and cyanosis and the patients often comment on the relief obtained by this measure The intravenous administration of theophylline ethylenediamine 0 48 gm in 50 c c of 50 per cent glucose solution commonly has a pronounced effect on the dyspnea and frequently has a beneficial action on the pain (This dose 0 48 gm instead of 0 5 gm is given because for some reason it is the amount put into an ampule by several manufacturing pharmaceutical companies) This should be injected very slowly and may be employed two or three times during the 24 hours if the circumstances justify it Cases have been observed in which this medication was apparently a life saving measure

There seems to be considerable doubt regarding the use of digitalis It should always be prescribed when there is significant cardiac em

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of his cardiac disability In order to attain this objective the patient necessarily must know the means of safeguarding himself and remain under the general supervision of his physician Finally it should be borne in mind that coronary thrombosis represents the terminal stage of arteriosclerosis of the coronary vessels and that subsequent attacks frequently occur

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CHAPTER XIV-C

SWELLINGS OF THE LIMBS DUE TO LOCAL CAUSES

By JOHN HOMANS

Table of Contents

Anatomical and Physiological Considerations

The various edemas of the limbs which are not due to such general causes as cardiac or renal disease often seem rather mysterious in their origin and have never been very accurately classified * The truth is that edema espe

* Recently Allen has presented an elaborate classification of the lymphedemas but does not consider particularly the swellings associated with the various types of thrombophlebitis.

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In the case of the lymphatics however it is almost impossible to conceive of any push into these delicate vessels from either the capillary bed or the tissue spaces In the case of the veins as the heart is approached there is undoubtedly some pumping effect which results from the action of the heart itself and from the respiratory motions but this can have very little influence as far off as the extremities particularly the legs In the case of the lymphatics it is impossible to conceive of any suction effect whatsoever outside of that which may perhaps be felt in the thoracic duct

What mainly impels the returning fluid through both veins and lymphatics is muscular pressure acting upon soft vessels which are enclosed within somewhat elastic tissues In walking or running and indeed during any motion however gentle the effect of muscular activity upon the valved vessels is constantly to empty their contents in the direction of the heart There is undoubtedly an optimum state of muscular activity which must be somewhere between complete relaxation and very violent muscular effort but as to this nothing precise is known It is obvious however that the veins and lymphatics which are enclosed among the muscles within the aponeurotic sheath have a decided advantage over those outside for muscular action upon them is direct and efficient whereas upon those external to the aponeurosis it is only effectual insofar as the enclosing skin and fat are elastic As evidence of this the veins within the muscular sheath of the legs never become varicose whereas those external to the aponeurosis frequently suffer over-distention and a breakdown of their valvular mechanism Whether the lymphatics are subject to such a change is unknown

Anatomically the drainage system of the legs is additionally vulnerable in that it can very readily be obstructed in the region of the inguinal ligament and along the pelvic brim Since the veins come together here to form the common femoral and great iliac vessels obstruction in this bottle neck causes venous congestion of the entire leg There are of course collateral channels so that mere ligation of the common femoral external iliac or even common iliac vein does not necessarily lead to a serious venous congestion but if the obstruction is spread out over a sufficient area as by an extensive thrombosis the collateral channels are insufficient to prevent a very considerable and prolonged rise of venous pressure peripheral to the obstruction A moderate elevation of the venous pressure causes to accumulate in the tissue spaces a fluid of low protein concentration but as the venous pressure is raised this fluid s percentage of protein correspondingly rises and finally when local asphyxia and capillary damage become extreme it may reach a height of three or four per cent (half that of the blood protein) and contain red blood corpuscles as well (De Takats) Thus venous obstruction if sufficiently prolonged and severe leads to an edema which because of its high protein concentration

cially of the ankle is rather readily brought about by a variety of local causes or to put it another way, the border line between swelling and normalcy is narrower than is generally supposed One might cite for instance, the effect of an injury such as a sprained ankle Here the initial swelling is in the nature of an exudate, but subsequently, that is, long after absorption of the exudate and repair of the torn ligaments, a tendency to swelling of the foot and ankle may persist for months or even years, in which case it must be believed that the mechanism for forwarding fluid against gravity has in some degree broken down There is also the edema which follows long confinement to bed or immobilization of a limb by a cast or splint Such may be counted functional and are perhaps more familiar though less disabling than those which have an organic basis Of these permanent and even progressive forms some are due to lymphatic obstruction others, to venous thrombosis and yet others to inflammatory conditions of a recurrent or chronic sort Cancerous metastasis is another cause of edema, especially when infiltrated lymph nodes have been surgically removed There are also hemangiectatic and lymphangiectatic congenital enlargements Such being the commonest causes of edema confined to one or more extremities it is pertinent to discuss the means by which the limbs normally keep themselves free from swelling that is by which they return to the heart the tissue fluids brought them by the arterial circulation

The veins and lymphatics divide between them the labor of draining the limbs In a general way the veins accept from the tissues only fluid of very low protein concentration while the lymphatics accept a considerable variety of substances including fluids of high protein concentration extravasated red blood corpuscles and particulate foreign material

Both the veins and lymphatics constitute closed systems which exchange fluids with the tissue spaces on physio-chemical principles * Both systems are freely supplied with bicuspid valves so arranged that fluid can pass them only in the direction of the heart In a general way, the more delicate the vessel the more abundantly is it furnished with valves and this is consistent with the mechanism by which when the limb they drain is dependent, these vessels are emptied up hill In the case of the veins, blood undoubtedly is pushed into them from the capillary bed though it is hardly possible to believe that the capillary pressure is ever greater than or indeed as great as venous pressure

* It will be recalled that according to the principles laid down by Starling low concentration of serum protein and a reduced colloid osmotic pressure in the blood cause fluid to escape into the tissues and forbid its absorption into the venous side of the capillary bed Nutritional and nephrotic edemas are of this sort while inflammatory edemas presumably are due to increased capillary permeability and raised capillary pressure The edema of cardiac weakness is probably a combination of venous congestion with malnutrition and low serum protein concentration

their supporting structures to cooperate with muscular pressure in forwarding fluid toward the heart may be a purely local process or may exaggerate a general cause such as failure of the heart's action and even in the absence of any organic obstructive factors the border line between a normal return flow from the legs and an accumulation of fluid is not a wide one as is shown by the examples of functional sorts of edema described at the beginning of this chapter

It would be very difficult to name all the conditions outside of cardiac and renal disease which lead to swelling of the limbs but barring those states they may be divided between (1) disorders primarily of the venous return and ( ) disorders primarily of the lymphatic return In making this distinction it must be admitted that there are border line conditions and states difficult to classify as in any little explored field Among the disorders of the venous return must be included varicosity and the various sorts of thrombosis and thrombophlebitis Among the disord rs of the lymphatic return there must be included the various elephantiases and the congenital lymphangiectases Among the swellings mainly functional and difficult to classify there must be counted those which result from injuries from deformities from inefficient use of the musculature and from congenital circulatory malformations of a combined sort.

The arm are only very rarely the seat of an axillary thrombophlebitis but occasionally present a high degree of lymph edema following removal of the axillary lymph nodes in operations for mammary cancer

Swellings Due to Disorders of the Veins

Varicose Veins

Varix the commonest of all vascular dise es is actually the cause of very little swelling in the sense of edema but represents rather an accumulation of blood in dilated superficial veins The vessels affected are entirely superficial to the muscular aponeurosis and the failure of varix to cause any notable amount of stasis and edema is due to the efficiency with which the abundant deep veins among the muscles are able to accommodate in addition to their natural allotment not only the blood which ordinarily would be carried by the superficial veins but such blood as actually pours down the valveless varicose veins One need never in the presence of varix worry about the state of the deep veins so lon as the ankle is not swollen and the foot is not cyanotic Indeed compensation for superficial varicosity is very rarely absent and only appears under abnormal conditions that is when the varicose individual must stand for unusually long hours or must carry on heavy muscular work for considerable periods without being able to elevate his legs For failure of compensation that is cyanosis and swelling of the foot elevation is only a

encourages tissue proliferation and fibrosis permanent changes of a fibrotic sort being created

The anatomical peculiarities of the lymphatic system are closely related to those of the veins The principal arteries and veins of the limbs are accompanied by a number of large lymph trunks which actually run within the arteriovenous sheath In the superficial tissues the principal lymphatics likewise tend to accompany the veins though a great many of them pursue an independent course in the same subcutaneous plane There are in addition smaller lymph passages in the form of networks and long fine cutaneous vessels which are in no way associated with the superficial veins At the groin all these systems come together passing through the various lymph nodes in the inguinal region and then as large constantly anastomosing trunks winding about the great artery and vein of the pelvic brim to reach the receptaculum chyli Thus the entire flow of lymph from the leg may conceivably be blocked in the same region in which obstruction of the venous system becomes so effective Moreover by their very close association with the great vessels about which they wind the deep lymphatics may become engulfed in perivascular inflammatory reactions or may themselves impart inflammation to the walls of both arteries and veins

The same arrangement is present in the arm, but for some reason the trunk lymphatics of the axilla seem particularly liable to injury in such dissections as are made for malignant tumors of the breast This peculiarity can not be laid entirely to cancerous infiltration in these cases Swellings occur after such axillary dissections as are made for mammary cancer even though the growth has not actually invaded the nodes

Lymphatic obstruction is not readily brought about by infections of the lymph nodes through which the lymph vessels must pass or even as a rule by rather extensive resections following such diseases as lymphogranuloma inguinale or tuberculosis To be sure the lymphatics are capable of being obstructed in filarial disease and doubtless by other very chronic and recurrent states of infection Such states, however must exist for an exceedingly long period before they are able to overcome the natural persistence of these vessels in maintaining their continuity and permeability The effect of lymphatic obstruction once established is rather different from that of venous obstruction, in that it results in a much more generalized fibrosis and enlargement of the extremity than ever occurs as a consequence of venous obstruction alone, that is the remarkable state of elephantiasis

The anatomical and physiological considerations just described indicate that blood and tissue fluids are carried from the dependent limbs principally by the effect of muscular activity upon valved vessels the walls of which though tough are only slightly elastic A failure of the valved vessels and

their supporting structures to cooperate with muscular pressure in forwarding fluid toward the heart may be a purely local process or may exaggerate a general cause such as failure of the heart s action and even in the absence of any organic obstructive factors the border line between a normal return flow from the legs and an accumulation of fluid is not a wide one as is shown by the examples of functional sorts of edema described at the beginning of this chapter

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temporary remedy compression by an elastic sort of bandage offers only partial relief and removal or obliteration of the varicose veins is the only cure There are various ways of bringing about this cure, which differ mainly in their permanence but while they last, all have this in common that so long as back pressure and stagnation in the superficial veins are abolished the deep veins are thereby relieved of an unnatural load Thus the relief of varicosity must always be of benefit to the return circulation and can never add to the burden of the normal deep veins

Complications — The complications of varicosity most likely to cause swelling of the leg are ulceration and thrombophlebitis Ulceration is a natural result of back pressure and malnutrition Once established it sets up a vicious circle of infection edema and induration It is capable of relief by skilfully applied local pressure and bandaging but its treatment usually is surgical Except when it encircles the leg an ulcer causes only local edema A ring ulcer however may give rise to elephantiasis

Thrombophlebitis in varicose veins results primarily from malnutrition in the wall of the varicose vessels, though in many cases there is undoubtedly a contributory infection The disease is a local one and, since it interferes in no way with the functioning deep veins of the leg causes only local swelling Its recognition is not at all difficult Somewhere in the course of an obviously varicose great saphenous vein usually in the lower thigh or upper calf there will appear a firm thickening sensitive to the touch If the thrombosed stretch of vein is very close to the surface the overlying and adjacent skin will show signs of inflammation usually of a mild sort That is it becomes a little edematous and somewhat discolored rarely a bright red As a rule, even if the thrombosed vein is not actually palpable in the heavy fat of the upper thigh the process can be counted on to extend to the saphenous opening Here it seems to stop cleanly so that the extension of a loose thrombus into the femoral is very rare indeed Indeed it is worth noting that, as compared with other forms of thrombosis that of varicose veins is adherent and little given to embolism Its most annoying feature is the prolonged disability which it causes It is susceptible of permanent relief by surgical measures which are rather too seldom used and a fatal embolism can always be prevented in the rare event that small emboli are continually being detached, by division of the saphenous vein at its entrance into the femoral Indeed, this step, even without others tends to shorten if not actually cure the disease

Thrombophlebitis Femoral and Iliac Phlegmasia Alba Dolens Milk Leg

The sign manual of this disease is the sudden swelling of a leg from toes to groin and buttock Edema begins in the periphery and rapidly works toward

the body Should both legs be affected one almost always swell considerably before the other so that a systemic cause of edema is not suggested No other swelling is of nearly so rapid an onset Phlegmasia alba dolens above all other sorts of venous thrombosis calls for an examination of the many influences which appear to lead to thrombosis in general

Thrombosis within veins is likely to result from an association of a group of factors which are often known as Lubarsch s tripos and these factors may be present in a great variety of medical surgical and traumatic states First there are the inflammatory and degenerative changes due for the most part to acute diseases which may affect the quality of the vascular endothelium Second there are the diseases and conditions which may alter the character of the blood that is toxemias states of dehydration chronic nephritis diabetes the puerperium and the vaguely understood conditions which result from the traumatism of accidents and surgical operations And third the states of sluggish circulation which accord the two previously mentioned influences a particularly good chance to act namely decompensated cardiac disease cancerous cachexia debilitating chronic infections and indeed almost any serious disorder or injury which causes prolonged confinement to bed

In addition to such factors as these there are in the case of the lower limbs anatomical peculiarities which seem to favor thrombosis at the very spot where it can do the most harm that is in the upper femoral and iliac region Here there are one or two large valves and many entering branches to cause eddies confuse the current and favor that deposition of thrombocytes which is the first step in the building of a thrombus It has been pointed out that in addition to these mechanical factors the current is apt to be slowed by increased abdominal pressure and perhaps by a sitting position in bed

Following childbirth the already congested venous system of the legs is subject to yet another hazard through its connection with the great uterine vessels Thrombosis from these veins may actually progress into the common iliacs though it is by no means clear that the thrombophlebitis of milk leg is not due rather to peculiarities of the blood itself combined perhaps with the effect of confinement to bed

Another important thrombophilic influence is injury As a result of serious falls fractures and surgical operations there is apparently created a tendency to thrombosis which may reveal itself in those parts of the body most liable to this happening Such may be called an indirect effect of injury There is also a direct effect For instance when a deep thrombosis follows a fracture of the neck of the femur it will occur almost invariably on the side of the fracture even though the treatment which has been instituted will have caused quite as complete immobilization upon the side opposite the fracture as upon the fractured side

It is not necessary to hold that there is any one primary cause of femoral and iliac thrombosis which acts especially from within the vein or outside it, but one must admit that the disease has become increasingly common under the very circumstances which are generally thought to lead to an improved treatment of serious illness namely, rest in bed The site of such a thrombosis as already explained is almost always that part of the great vein draining the leg which is situated near and above the inguinal ligament, that is it is a deep femoro iliac thrombosis — phlegmasia alba dolens

Pathological Features — Whatever the influences which cause it to occur phlegmasia alba dolens represents a more or less extensive thrombosis, which apparently begins near the pelvic brim, and the effect of this thrombosis as already explained is necessarily to cause a swelling of the entire leg There is seldom anything septic about this process, the thrombus being as a rule solid often cleanly bitten off at its proximal end but extending for a variable distance downwards into the venous tree of the leg It is probable that the more severe and persistent swellings are due to very extensive thromboses and that the more temporary swellings are due to thromboses of relatively short extent within the vessels Naturally the venous circulation finds it difficult to circumvent the more extensive thrombus and relatively easy to circumvent the more local one Moreover the extensive ones are only slowly canalized by the processes which finally restore some sort of lumen to the vessels and the short thromboses are rapidly canalized Surgical explorations (Homans) have demonstrated also that in some instances, the lymphatics as well as the veins are involved in these processes but exactly how the two systems are related to the degree and duration of the swelling is not understood In some cases there is a violent perivascular reaction about the great vessels along the pelvic brim including vein artery and lymphatics In other cases the thrombosis in the vein is unattended by any perivascular reaction whatever though even here an associated thrombosis in the lymphatics has been noticed

The *clinical manifestations* of phlegmasia alba dolens, though varying from case to case are always recognizable The disease often begins with very acute cramp-like pain referred to the groin the inner side of the thigh or even the back of the knee and calf At other times the onset is very quiet, a sense of heaviness at the most being noticed As a rule in the initial stage even before other signs appear the pulse is elevated Within 24 to 48 hours swelling shows itself at first in the ankle and rapidly mounts to the inguinal ligament and the fold of the buttocks In the milder cases the swelling is so moderate that the leg pits readily on pressure and the patient is able to move it without much discomfort In the most severe cases tension is such that the leg no longer pits on pressure and voluntary movement is impossible The degree of fever is extremely variable but there is almost always a moderate elevation

which lasts for at least a week Rarely a fever of 101 to 102° F may persist even for months

One peculiarity of the disease which has seldom been discussed is its tendency to be bilateral and though it is true that one leg the left as a rule appears in most cases to be the sole seat of the trouble certain post phlebitic complications reveal the fact that the second leg has often been affected by a very mild form of thrombophlebitis altogether overshadowed by the more obvious disease in the first There is also some tendency although the leg is usually *white to a slight degree of pinkness which may take the form of* streaks or blushes suggestive of a mild lymphangitis A rather confusing feature of phlegmasia alba dolens is the tenderness over the deep femoral vessels which is most notable in the groin but which may extend down even to the calf This sometimes gives a false impression of superficial thrombophlebitis since the great saphenous vein overlies the deeper vessels It should be recognized however that whenever the whole leg is swollen a deep femoral and iliac process must be present

Treatment —There has grown up in the course of years a feeling that since phlegmasia alba dolens occasionally gives rise to pulmonary embolism the patient must be kept particularly quiet and the leg immobilized The fact is that movements of the leg itself probably have nothing whatever to do with the detachment of an embolus which must almost necessarily break from a propagating thrombus waving in the current at the proximal end of the process that is within the abdomen Thus if such a thrombus is present an embolus can be detached at any time whether or not the leg is quiet and on the other hand when the proximal extremity of the thrombus is solid and cleanly healed there is no possibility of embolism On the whole therefore immobilization is of little value is more likely than otherwise by slowing the venous stream to lead to a spread of thrombosis toward the heart and is undesirable on the ground that it prevents the escape of tissue fluids from the leg Moreover since an accumulation of tissue fluids which in severe degrees of obstruction as already explained are highly proteinized is apt to lead to fibrosis of a permanent sort especially in the calf of the leg there is every reason as DeTakats has pointed out for elevating the leg well above the body and for trying by every legitimate means to relieve it of its excessive edema It is particularly unfortunate therefore that in the face of cardiac decompensation renal disease postoperative convalescence local injury by fractures and debilitating states in general it seems impossible or at least undesirable to place the patient in the position best suited to drainage of the leg that is with the upper end of the body depressed and the legs elevated One can only occasionally raise the leg upon an inclined plane or suspend it on some form of *splint* One can however when the acute stage of the process is past and

movements of the leg, both active and passive, are possible, exercise the leg in bed in an elevated position, thereby aiding the disposal of its excessive fluid and restoring its normal circulation Such movements have, in the past too seldom been attempted

The *after effects* of phlegmasia alba dolens may take one of two forms and in some instances the two may be combined These are *residual edema* and *post phlebitic induration and ulceration* Not infrequently residual edema of some degree continues to trouble the patient more or less during the remainder of his or her life The swelling may only occur upon long hours of standing and may change very little as the years go on On the whole there is a tendency for such swelling as is evident when the patient begins to get about to diminish with time so that what often looks like a very troublesome situation may in the course of six months to several years be very much improved In fact post phlebitic swelling is not the most serious complication of phlegmasia alba dolens

Induration and *ulceration* often are very serious indeed The first sign of trouble is apt to set in within six months to a year following the thrombophlebitis but may be delayed for two, three, five or even ten years during which interval the patient appears, except for a very slight residual swelling, to be entirely well The induration usually is ushered in by a localized edema associated with an area of hardening of the subcutaneous tissue, the skin being normal in color or slightly reddened In other instances a local area of pigmentation appears upon the leg and, as this spreads, the subcutaneous tissues gradually become indurated In either case the change almost always occurs first in the inferior half of the lower leg more often on the inner side than the outer occasionally in the region of the malleoli Thus, it occupies the position of many varicose ulcers and is often judged to be a result of varicosity in spite of the fact that varix is entirely absent * However, the indurated area or areas may appear in bizarre positions as for instance on the back of the calf or on the outer side They are never seen in the thigh

The development of ulcer in such areas is generally a matter of accident. The patient suffers a blow or makes a scratch The resulting ulceration, once established is very obstinate and tends to spread over an ever widening area There is nothing remarkable about the appearance of the ulcer itself the factors which identify it being found in a history of a previous phlegmasia alba dolens and in the sort of onset already described A noteworthy feature of these ulcers is not only their intractability but their painful quality the

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most agonizing of all being those in the region of the internal malleolus In deed the painful nature of these ulcers has caused them in the past to be spoken of as irritable ulcers It must be supposed that they are the result of secondary non suppurative infection acting upon tissues whose resistance has been lowered by the serious stasis of the original thrombophlebitis Other wise it is impossible to explain the very late onset of some of them Their course is almost invariably one of persistence and extension the breaking down of tissue following the spread of pigmentation and induration In some instances the process encircles the leg but, though it may occupy a considerable area in the lower two-thirds it never mounts to the region of the knee

Treatment of Ulceration — It should be the object of every patient who has suffered from phlegmasia alba dolens to protect the legs against induration and ulceration by a very gradual resumption of an active life after the initial disease appears to have subsided It will be wise if swelling persists to use an elastic stocking or to apply a semi elastic bandage It will certainly be of advantage in case some small thickening or induration appears to apply elastic pressure and keep the leg elevated even retiring to bed until the local area resumes a normal appearance Undoubtedly persons who are able to avoid long hours of standing are better able to escape these complications than those who must necessarily look after a household or pursue a laborious occu pation

Once established ulceration is very difficult to control Local elastic pres sure as by a rubber sponge may be of advantage and under rest and skilful treatment the ulceration often can be healed But there is such a tendency to recurrence that more radical surgery usually is required This consists in the surgical excision of the involved area however large and the application of some form of skin graft It will always be found that scar formation has extended down to the muscular aponeurosis which must therefore be removed in order that the skin grafts may be placed upon the normal tissues beneath (Homans) A very useful palliative measure is the division of the nerve supply to the region of the painful ulcer Just why the ulcer should have a tendency to heal when the pain is relieved by nerve division is not clear There is no proof that a division of the local cutaneous nerves causes any permanent vaso-dilatation

The following are illustrative cases the first being an extraordinarily mild one and the latter one of unusual severity

Case I A married woman of 33 the mother of four children had given birth to twins seven years before coming under observation Four weeks after her confinement she developed a milk leg The swelling was most noteworthy in the left leg but there was sufficient swelling in the right to show that the process was bilateral Ever since that time there had been slight swelling of

movements of the leg both active and passive, are possible, exercise the leg in bed, in an elevated position, thereby aiding the disposal of its excessive fluid and restoring its normal circulation Such movements have in the past too seldom been attempted

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Deep thrombosis or thrombophlebitis in the calf is apt to be brought on by rather trivial things such as local injury, a minor fracture in the foot or a fall It has also been known to occur as a complication of acute respiratory illness and acute rheumatic states Apparently the extraordinary abundance of the collateral anastomotic venous channels among the great muscles of the calf offers an opportunity for a thrombosis to wander about for weeks perhaps without sufficiently obstructing the return circulation to bring out any physical signs whatever when the leg is elevated and not in active use and to cause some degree of cyanosis and swelling of the ankle only when the leg is dependent and in use In some cases the process invades one of the principal veins and enters the popliteal vessels in the form of a loose propagating thrombus When this occurs a fatal embolism is almost certain to follow In other cases the thrombosis after remainin for some time confined to the calf rather suddenly extends up into the femoral and even the iliac vein causing a general swelling of the leg quite like that of phlegmasia alba dolens As already explained an unusual event of this sort throws considerable light upon the nature of the ordinary type of deep thrombophlebitis which by contrast commences in or near the pelvis Finally in many instances thrombosis among the deep veins of the calf ceases to extend and upon rest in bed for a week or two heals completely leaving little or no trace behind

The difficulty in treating such a disorder lies in one s inability to predict the course of the disease that is whether it will result in healing extension or fatal embolism It would appear wise therefore upon identifying the early signs of this state to place the patient in bed keeping the leg elevated though not completely immobilized for some ten days At the end of this time a semi elastic bandage being applied from toes to knee the use of the leg should very cautiously be resumed And if in the course of the next week improvement continues and swelling and cyanosis of the ankle do not recur the process may be considered healed

Should such treatment on the other hand be followed by a recurrence of the original symptoms ligation of the femoral vein just distal to the entrance of the great saphenous would appear to be a reasonable procedure It is unlikely to give rise to an extension of the thrombosis and certainly prevents embolism provided a long propagating thrombus has not already mounted high in the femoral* However one may feel about subjecting a patient to

It should be remembered that the long propagating thrombus gives no sign of its presence since the current of blood is able to pass around it Instances have been observed in which a loose thrombus some ten to twelve inches long has caused a fatal embolism when the presence of even a local deep thrombosis in the calf was quite unsuspected Indeed it s remarkable how silent provided the patient remains in bed a deep peripheral thrombosis associated with a long propagating thrombus can be

the left ankle, especially in hot weather and on considerable standing about Exercise had had rather a favorable influence

For several weeks she had noticed, above the internal malleolus an area of slightly indurated swelling about cm in diameter, which was slightly sensitive to the touch The foot in general showed a faint pinky blueness which was not present on the other side

As a result of keeping off her feet and wearing an elastic stocking the swelling and induration completely disappeared but on taking a long walk recurred again

Case II A single woman of 50 had been operated upon 17 years before for an acute appendicitis Deep thrombophlebitis occurred when she was beginning to sit up The process was bilateral showing itself first in the right leg The onset was associated with considerable pain Two to three weeks later, when the right leg was beginning to improve, the same thing occurred on the left

Within a year after the onset of the deep thrombophlebitis areas of pigmentation had appeared in the left leg and one of these broke down to form an ulcer This healed and it was many years before another occurred

The picture presented by the patient sixteen years after the onset of the phlebitis was that of a very considerable swelling of the lower leg with an area of extensive induration and ulceration nearly encircling it The right leg was less swollen less indurated and only presented one or two areas of pigmentation It was necessary to operate twice on the left leg before healing was secured and a very extensive excision skin graft and plastic was required In the meanwhile an ulcer occurred on the right leg which required less radical treatment

Later this patient was gored by a cow who applied her horns to the grafted area tearing it badly However, healing eventually followed

Deep Peripheral Thrombophlebitis — This state is little understood Though unusual it is probably more common than has generally been supposed and is identified by a peculiar symptom complex, namely one of moderate swelling and blueness of the ankle and lower leg never the thigh, signs which are quite evident when the patient attempts to get about which disappear rapidly and perhaps completely upon elevation of the leg in bed, but which recur over and over again in some instances upon attempts to resume a normal life This form of thrombosis offers evidence that the typical phlegmasia alba dolens does not originate in the lower leg for when as occasionally happens the peripheral deep disease progresses into the femoral and pelvic veins the change in its character is unmistakable Then the edema of serious obstruction from being confined to the lowest portion of the leg pervades the whole limb and the swelling as in phlegmasia alba dolens becomes persistent instead of intermittent

itself can be felt as a cord like mass over which the skin is slightly raised even reddened Such a local process may be more or less symmetrical in the two limbs and tends to recovery within a week or two but there is usually a jump to a higher level the process being repeated several times nearer the root of the limb on each occasion There is very little tendency to embolism from such a phlebitis which supports the hypothesis that primary inflammation of the vein s wall leads to the firm fixation of the thrombus

Thrombophlebitis in otherwise normal superficial veins that is in non varicose veins and in the absence of thromboangiitis obliterans occurs more freakishly than other sorts of thrombosis It rarely appears as a complication of child birth bed life fractures or surgical operations as is the case with phlegmasia alba dolens It is usually confined to the great saphenous system and only when it occupies a considerable part of that system does it lead to swelling of any consequence

The initial sign usually is a somewhat painful tender thickening of some part of the great saphenous system in the thigh or calf that is on the inner anterior face of the lower limb The skin over the thrombosed vein is often reddened Rarely much of the saphenous tree is outlined in this way and then the area so defined may be diffusely and moderately swollen More often the disease remains local or progresses slowly upward or downward from its point of origin The thrombosed vessel can readily be palpated

The tendency of such a thrombosis under rest is toward healing but embolism is relatively more common than from thrombosed varicose veins Moreover the process is capable of entering the femoral in which case an accession of pain in the region of the groin may occur and the whole limb becomes swollen though to a lesser degree than is the case with phlegmasia alba dolens Whether either of these latter accidents can be forestalled by any particular treatment is difficult to say The thrombosis is apt to progress under complete immobilization and very active exercise certainly predisposes to embolism Some compromise between these extremes that is the application of a light semi-elastic bandage and limited exercise probably is advisable The traditional use of ice is without merit

The following is an instance of a serious form of the disease

Case I A man of twenty-eight at the end of a long seige of whooping cough noticed a local painful tender pencil like thickening on the inner face of his right thigh He applied adhesive plaster and played a hard game of squash racquets Within a few hours his respirations became embarrassed he began to expectorate fresh blood and a considerable area of dulness appeared at the base of the right lung Under rest in bed the area of infarction slowly cleared up and the bloody expectoration gradually ceased but some ten days later to the accompaniment of pain in the groin the whole leg

high division of the femoral vein it must be admitted that such treatment can have no permanently bad effects upon the circulation Those who have seen the operation performed in instances of peripheral thrombosis report themselves as more than satisfied with the result and those, who have seen their patients die of pulmonary embolism without high division, naturally regret that this precautionary measure has not been taken

The following are illustrative cases

Case III A healthy, athletic man fifty years of age, suffered a contusion of his left foot which fractured his fifth metatarsal bone A plaster cast was applied for a week after which crutches were used for six weeks During the two succeeding months he exercised as usual, but his leg was always uncomfortable Four months after the accident the left ankle was found to be swollen but after a few days rest in bed seemed again quite normal Again he went about again swelling and blueness of the lower leg returned and again rest restored a normal appearance Four and a half months after the original injury he died of pulmonary embolism Autopsy showed an extensive thrombosis of the great plexuses of veins serving the muscles of the calf A propagating thrombus had penetrated into the popliteal where finally it had broken off giving rise to an embolus six inches long Femoral ligation at the groin would have forestalled the fatal embolism

Case IV A woman of forty three years nine weeks before coming under observation twisted her foot suffering an oblique subperiosteal fracture of the fifth left metatarsal bone She remained in bed for ten days after which upon getting about she noticed discomfort in the left calf and swelling of the ankle On returning to bed all signs disappeared, but on attempting to walk again the swelling returned When seen at this time, the foot appeared faintly cyanotic Only below the external malleolus was there a little edema Two months after the accident the femoral vein was divided just distal to the entrance of the great saphenous Complete recovery followed and persisted

Superficial Thrombophlebitis (Non varicose) — This state is included among other forms of thrombophlebitis principally for the purpose of explaining that by itself it does not cause swelling of the leg It takes either of two forms (1) phlebitis migrans a more or less specific disease frequently an exhibition of thromboangiitis obliterans and (2) thrombophlebitis in otherwise normal superficial veins an uncommon and accidental disorder

Phlebitis migrans appears to be a true phlebitis that is a disease of the vein s wall though occasionally it is seen as a recurrent condition in individuals whose blood seems to have an unnatural tendency to thrombosis, and as to whom it is difficult to say whether the primary thrombosing factor lies in the vein s wall or its contents Phlebitis migrans tends to occupy a short length of a peripheral vein almost invariably on one or more limbs The vein

that of dragging about a heavy limb unless there are added to the chronic edema and fibrosis the remarkable attacks of so-called lymphangitis which many incorrectly believe to be necessary to the development of the disease As a matter of fact they often set in both in tropical and other forms only after the condition is already well established

Varieties of Elephantiasis — There are certainly according to their mode of origin four sorts (1) *Filarial elephantiasis* This is most common in the tropics presumably is due to a very chronic infestation with Wuchereria Bancrofti and very likely is favored in its development by the abundance of bacteria of all sorts which abound in hot climates In these days of free communication with tropical countries it is seen more often than formerly in the large cities of temperate regions (2) *Sporadic and familial elephantiasis*, forms which are exactly alike pathologically and clinically and which quite possibly result from similar defects in the lymphatic system The familial form is known as Milroy s or Meige s disease (3) *Elephantiasis dependent primarily upon chronic bacterial infection*, a sort which presents a greater variety of appearances than the others in that there may be lesions in the periphery of the limb indicating a source of bacterial infection as for instance, chronic ulceration or perhaps merely epidermophytosis This sort includes those enlarged limbs which result indirectly from phlegmasia alba dolens (4) *Surgical elephantiasis* a variety not at all uncommon in the arm after operations for cancer of the breast but which may conceivably occur as a result of extensive disease of the inguinal and pelvic lymph nodes This last variety deserves very little consideration so far as the legs are concerned though it is conceivable that some of the endemic elephantiases are due to inflammatory diseases of the lymph nodes in early life so quiet as completely to have been overlooked

Filarial Elephantiasis — An individual may be heavily infested with filaria without suffering from any swelling and it has even been shown by O Connor Golden and Auchincloss that the subcutaneous tissues can be filled with calcified filarial organisms without presenting any appearance of disease whatever Elephantiasis may be confined to one limb or develop in both legs Occasionally it even involves at one time both legs the scrotum and the arms Apparently after many years of filarial infestation the lymph channels not only in the bottle neck at the root of a limb but in the entire extremity often end by being destroyed and this destruction presumably includes both lymph nodes and lymph vessels Large groups of lymph glands are sometimes filled with great distended lymph spaces but such conditions are seldom seen in temperate regions Ordinarily the limb presents that appearance of swelling with hypertrophy of the skin and subcutaneous tissues which is described at the beginning of this section Ulceration is

became heavy and moderately edematous At this time the main radicals of the great saphenous vein could be felt as solid cords Evidently an embolus of moderate size had been detached before the obstructing thrombosis had extended into the femoral vein When last seen the patient was making a good recovery

Thrombophlebitis in the Arm — This disease, which is rare has been so little studied that almost nothing seems to be known of the circumstances under which it arises The only instances observed by the writer have been left sided One was associated with an attack of acute tonsillitis and a non suppurative acute axillary adenitis The other occurred in an individual who had long suffered from acne vulgaris Thus infection may have played a part in both cases Both patients were young and active men

The swelling develops in the course of some three days associated with stiffness at the elbow and noticeable cyanosis There is only a moderate rise of temperature As might be expected the disease is short lived as compared with phlegmasia alba dolens Indeed the process may run its entire course in three weeks Rest in bed with elevation of the affected arm on a pillow appears to be a satisfactory treatment

Swellings of Lymphatic Origin

Elephantiasis

Swellings due to disorders of the lymphatic system in contrast with those for which thrombophlebitis is responsible are almost invariably of slow development and chronic course Although elephantiasis may arise in several different ways the ultimate result is always much the same and the appearance of the limb is unmistakable Edema is first noticed in the lowest part of the extremity and gradually mounts so that in the case of the leg the entire limb to the level of the inguinal ligament in front and the buttock behind finally becomes edematous Usually the development of the swelling is spread out over some years though rarely it may be quite complete in the course of a few months However it is the changes secondary to chronic edema which give the disease its peculiar character In the course of time the subcutaneous tissues develop such induration that pitting ceases and the skin becomes hypertrophied taking on first a peau d orange appearance and even, in exceptional instances being thrown into actual papillary masses Later the great thickening of the subcutaneous tissues leads to the formation of rather large folds which in an extreme form of the disease may be creased in rather bizarre ways There is almost always a crease at the ankle particularly when a shoe has been worn constantly The patient suffers no inconvenience other than

It has been shown in the experimental animal and in some cases in man that the peripheral lymphatics of the leg are incapable of surviving a prolonged obstruction Probably then it makes very little difference whether elephantiasis is held to be a disease of primary occlusion of the lymphatics within the pelvis or a generalized destruction of the lymphatics of an altogether unaccountable sort For in the end no lymphatics deep or superficial are likely to be left in the elephantiatic leg The circulation of fluid must therefore be through tissue spaces by gravity Indeed it can sometimes be demonstrated that a dye will quite rapidly pass up or down the leg as the case may be in the deep skin where pathways developing from the remains of lymphatic networks or from dilated tissue spaces, are present Such fluid as escapes from the leg undoubtedly reaches parts of the body from which normal drainage is available

The *febrile attacks* which occur in a moderate percentage of all elephantiases are more common in the tropics where bacteria are rife than in temperate regions However they may occur at any stage of the familial or endemic disease in an unpredictable manner There is no ground for the assertion made by some that the attacks are essential to the development of lymph stasis Moreover there is ample clinical evidence that a high degree of elephantiasis can develop in their absence And there is experimental proof (Drinker, Field and Homans) that the attacks are able to commence automatically in an animal s elephantiatic limb From the tissue fluid of such a limb non suppurative streptococci can be secured while the attack is developing but for only a short time after the fever has reached its height and never between attacks This accounts for the difficulty of demonstrating bacteria in human beings since, as a rule a patient is seldom available for critical study in an early stage of an attack

The name lymphangitis which has so often been used to describe these violent episodes is almost certainly improper since as already explained no lymphatics are likely to be present in the elephantiatic limb However the attacks nearly enough resemble acute sorts of reticular lymphangitis to make the term intelligible There is a rapid rise of temperature with which chills usually are associated There is prostration and painful swelling of the entire leg The skin is reddened and hot but without abscess formation of any sort

Treatment of elephantiasis at the present time is not particularly successful On the whole the most satisfactory means of dealing with the disease is to excise as completely as possible the elephantiatic tissue of the lower leg especially replanting the skin upon the normal deep parts in a series of operations There is no such thing as restoring lymph drainage within the leg itself Nor can tissue fluids be introduced among the muscles as Kondoleon and others have attempted to do Whether even the ingenious procedure of

never a feature and indeed, the skin of elephantiatic individuals seems to heal after trivial injuries and infections in a quite normal way

In tropical regions attacks of lymphangitis are very common Each attack is self limited lasts a few days is marked by very high fever and by local redness and increased swelling of the part The individual usually is prostrated Such attacks are apt to occur more often in hot weather than cold and seem to be precipitated by over fatigue and by trivial depressions of various sorts including in women the catamenia They will be discussed further in the following section The treatment of tropical elephantiasis is surgical and will be described with that of the sporadic and familial forms

Familial Elephantiasis (Milroy s Disease) and Sporadic Elephantiasis (Elephantiasis Nostra) — There have been a number of reports of families many of whose members for several generations have suffered from elephantiasis of the legs Those of Milroy and Meige have been very striking and have given the name to this remarkable state In the family described by Milroy the disease was not only familial but congenital Such has not been the case in other instances Strange as it may appear, the etiological factor has remained completely unknown, probably because those suffering from elephantiasis always die of some entirely different complaint and thus are not subjected to critical study at autopsy As far as can be learned, there is no pathological difference between the familial disease and the sporadic instances of elephantiasis which occasionally crop up

The edema of the familial and sporadic types commences as a rule at about the time of puberty occasionally in early adult life or in childhood and rarely in infancy or middle age It appears insidiously, at first in the ankle Many years are required before the full development of the typical serious deformity is reached Indeed some cases never go beyond such a degree of swelling as is often seen in the ordinary milk leg In a family reported upon by Hope and French many of the individuals were able to control the edema by means of bandages, while others suffered from a more severe form, to the accompaniment of serious febrile attacks, and were unable to control the swelling in any way

Familial elephantiasis is rather evenly divided between the sexes but to the sporadic form females are decidedly more liable than males One or both limbs may be affected At first the edema confined to the lower leg pits on pressure, but as the disease advances, the skin and subcutaneous tissues become so thick and tough that the surfaces of the leg can no longer be indented Early in its course the swelling completely disappears overnight upon rest in bed Later, residual edema is established At no time however does the maximum swelling persist during rest The leg is always capable of considerable reduction in size upon elevation in bed

uncontrollable it may even be necessary to desensitize the individual to the bacteria with which he is afflicted

The following examples include an elephantiasis which followed phlegmasia alba dolens but was probably aggravated by adiposity

Case VII W I C This man of middle age had for many years been troubled with an active epidermophytosis of his feet especially the right An indurated callus like area had long been present on the outer aspect of his right ankle and of course the usual intertriginous lesions Six to seven years before he came under observation he began to suffer from attacks of boils upon both legs It was then discovered that his blood sugar was high in amount (0 88 per cent) and when given insulin the boils cleared up A year later swelling of his right ankle was first noticed and because several large veins were present on this side sclerosing injections were used decidedly to his disadvantage During the past three years attacks of swelling redness and watery weeping in the right leg had set in associated with fever malaise and tenderness in the right groin These occurred perhaps three times a year and lasted for about a week In this period the whole lower leg had steadily become harder and more swollen The calloused scaly area had come to occupy the lower two-thirds of the leg

As a result of intensive treatment directed against the fungus the attacks have ceased but it is not yet known whether or not the epidermophytosis will recur and whether the swelling will in the end progress or recede

Case VIII I P An obese woman of thirty three had suffered from phlegmasia alba dolens of the right leg eighteen months before coming under observation Thereafter the edema never entirely disappeared One year later a very painful ulcer broke out just above the internal malleolus a typical post phlebitic sore This resisted treatment though division of its nerve supply caused it nearly to heal Since that time the leg had grown steadily larger and harder A new ulcer had appeared and persisted but there had been no clean cut febrile attacks Although the leg is greatly enlarged its hardness below the knee is everywhere the same which is not the case with a pure postphlebitic induration Obesity and chronic infection are probably contributing factors

Surgical Elephantiasis so far as the legs are concerned can hardly be said to exist It is easily recognized in the arm following operations for cancer of the breast where it behaves exactly like any other elephantiasis even to the febrile attacks Indeed it is the decided similarity between surgical elephantiasis as seen in the arm and other forms which show themselves in the leg which has supported the hypothesis that a definite obstructive lesion presumably is present at or central to the root of the limb in all elephantiases It has never been found possible to influence the course of surgical elephantiasis

Sir Harold Gillies, that of transplanting lymph bearing tissue from the arm to the thigh and body in such a way that the tissue fluids of the upper thigh are offered a way to the axilla will prove of any real advantage has not yet been demonstrated

Most of the sporadic cases encountered by the writer have developed at or considerably after puberty, that is, in the third decade and in one instance in the fifth Five have occurred in females Two instances in males brothers seem to represent the familial disease The following is an example of sporadic elephantiasis of an unusual severity

Case VI R S As a girl of 13 this patient first began to show edema of the right ankle The swelling developed rapidly, and two years later she suffered her first febrile attack At this same time the left leg began to swell A year later a violent attack associated with increased swelling and redness involved both legs This happened a week after her marriage During her ensuing pregnancy the edema increased alarmingly The external genitals became so tensely swollen that it was finally necessary to deliver the baby by Cæsarian section No ulcers or peripheral infections have ever been present At the age of 19 various operations were undertaken vulvectomy exploratory laparotomy, during which it was demonstrated that the principal pelvic lymph vessels and nodes were extensively sclerosed though no actual obstruction was demonstrated and a number of plastics upon the leg below the knee, by which thin, wide skin flaps were replanted upon the sub aponeurotic tissues of the legs over their entire circumference

The result of these procedures has been to reduce greatly the size of both lower legs and as an unexpected by effect, the thighs as well However the reduction of the size of the leg though it has made life bearable, has not lowered the high percentage of protein in the tissue fluids nor has it altogether done away with the febrile attacks

Elephantiasis of Bacterial Origin —As compared with other forms of elephantiasis, this form is not clean cut It is only likely to appear in those who present ulcerations of the leg or a focus of infection in the feet In this connection epidermophytosis may be a more potent source than has usually been supposed, for the tissues may not only suffer from the effect of direct streptococcal infection entering through the original focus but may actually be hypersensitive to the dead bacteria or fungi themselves In this latter case repeated outbreaks of fever swelling and ever increasing induration are uncontrollable so long as the initial infection persists It is perhaps enough to say of this disease that the tendency of the leg is to become enlarged and hard without exhibiting the usual insidious edema of other types of elephantiasis A source of infection in the periphery of the limb usually is obvious, and treatment should be devoted to dealing with such infection Should this be

of this sort it would seem advisable therefore to give them exercises to strengthen the muscles and tendinous structures governing the foot in order that the muscles may be used more effectively At the same time the leg should be elevated at every opportunity so that gravity may aid in evacuating the tissue fluids

Following long confinement to bed swelling often is quite serious at first It is even conceivable that if an individual fails to regain normal strength and activity the swelling may persist without any strictly organic lesion However it almost inevitably happens that after a few days or weeks of gradual increase in exercise and as the muscles resume their normal tone and strength the occasional swellings which appear after a long confinement to bed entirely disappear

In considering this rather vague and unsatisfactory group one must also have in mind some general conditions whether pathological or physiological which are known to bring with them a tendency to edema such for instance as obesity hot weather and pregnancy One must in fact be on the look out for an unexpected combination of many influences Consider for example the case of an individual one of whose feet is badly pronated who has perhaps paid little attention over many years to a slight swelling of this ankle only really appreciable in hot weather If now some nutritional cardiac or renal cause of edema becomes operative even in the very slightest degree the intermittently swollen ankle may become permanently edematous a unilateral phenomenon which at first sight seems very difficult to explain Many other such combinations might well be postulated

Circulatory Malformations

The angiomatous growths or rather malformations which occasionally occupy some part of a limb are necessarily laid down in uterine life and change very little afterwards growing with the individual Rarely are they entirely related to either the lymphatic or arteriovenous systems There is usually an association of vascular sinuses and abnormal veins with more or less lymphangiectatic tissue Angiomas of this sort usually have a neurogenic distribution occupying one or more dermatomes rather than the area supplied by any one peripheral nerve They may considerably deform the hand and forearm On the leg they are often greatly elongated extending from some point on the outside of the buttock as a more or less broad band downward in the direction of the foot However they may occupy areas more patchy than continuous or may pervade nearly the entire leg and in any case the swelling which results is almost necessarily confined to the region of the malformation itself and does not produce effects beyond it These peculiar and often very

with any more success than that of other forms Handley s excision of long strips of deep fascia and implantation of silk have not proved successful in the hands of most surgeons Theoretically, of course it should be possible if the point at which the principal lymphatic channels are interrupted is recognizable to lead the lymph past this obstruction by some plastic procedure It should be recognized however that since the peripheral lymphatics are almost certain to be destroyed by prolonged lymph stasis any such plastic procedure to be successful, must be carried out at an early stage of the disease

Allied to this form of lymphedema are those occasional cases of malignant tumor which by direct extension or metastasis and without being subjected to operation, prevent the escape of fluid from a limb Outside of cancer of the breast such tumors may include some malignant ovarian cysts occasional lymphoblastomas and doubtless others Whether the obstruction in such cases is lymphatic or venous or a combined form is always difficult to say Lymphedema due to obstruction by a new growth usually is progressive un remitting and of high degree

Edemas Due to Injury Deformity and Disuse

The edemas due to such causes are never very serious and usually are temporary It is quite conceivable however, that any one may become inter mittent or even permanent

A sprain of the ankle as already explained may be followed by edema The patient probably will have recovered so far as function is concerned in a perfectly normal way but moderate swelling of the ankle will persist Of course this is a rare occurrence It is impossible to guess at the exact cause of such an unfortunate result It must be supposed however, that sufficient injury is done to the local lymphatics to upset the rather delicate balance between normalcy and edema It is also possible that sufficient organic injury is done to ligaments and tendons to make subsequent use of the foot a little less vigorous and competent than before The writer has encountered patients in whom edema only appears on the injured side upon prolonged exercise or on very long standing Possibly this sort of swelling is allied to the appearance of varicosity in a leg of which the foot is somewhat pronated In that case one is left in some doubt whether the pronation is due to the varicosity or whether the varicosity is due to the poor use of the foot The latter alternative seems the most probable because the muscles of the lower leg never function so well when a person walks splay footed as when he walks normally and a normal emptying of the veins depends greatly upon muscular action In the same way edema may conceivably result from faulty mechanics of the foot and ineffi cient use of the muscles In dealing with individuals who suffer from edema

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unsightly deformities usually are marked by some slight discoloration of the skin and by a decided alteration in the consistency of the subcutaneous tissues They are not exactly mushy, that is, there is unlikely to be sufficient fluid at any one point to disappear on pressure but the surface is a little uneven and the normal feeling of the subcutaneous fat is lacking

Should such a malformation demand treatment it is seldom so vascular that it can not with safety be excised though the operation may have to be divided into many stages Actually, the procedure is a replantation of flaps of skin as thin as can safely be made, upon the tissues beneath the deep fascia In some instances complete removal is impossible or at least entails the excision of structures too valuable to be sacrificed, for in the hand especially the tumor may penetrate deeply among muscles, tendons vessels and nerves

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CHAPTER XIV-D

TUMORS OF THE CUTANEOUS GLOMUS (GLOMANGIOMAS)

By ORVILLE T. BAILEY

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INTRODUCTION

Subcutaneous nodules must have occupied the attention of physicians from an early date. To go back no farther than the eighteenth century there are among the writings of such authors as Camper and Morgagni[1] accounts of small painful tumors in that situation. Time and the microscope have demonstrated among them groups with similar histogenesis and clinical behavior. One of the most recent of such groups to be identified is that originating in the cutaneous glomus. In 1920 Barré[3] for the first time established the association of small tumors of the extremities with severe and intractable neuralgias, demonstrating that local excision of the tumors resulted in their permanent cure. It remained for Masson[19] in 1924 to demonstrate that these tumors take origin in overgrowths of the cutaneous glomus. These findings have been confirmed and extended by many authors until the condition has become a well established clinical and pathological entity. Of the various names which have been proposed for such tumors none seems entirely satisfactory. For that reason *glomangioma* has been suggested elsewhere[2] as a term indicating the blood vessel origin of the lesion and the specific unit concerned.

THE NORMAL CUTANEOUS GLOMUS

Since the appearance and behavior of glomangiomas depend on the peculiar properties of the cutaneous glomus, a brief description of the normal structure

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their connections with nerves Beneath the endothelium and usually separated from it by a few smooth muscle cells of the usual type are large clear round cells which are found only in the cutaneous glomus and its homologues the most important of which is the glomus coccygeum These cells in some instances form a syncytium

The glomus cells are derived from smooth muscle cells by a process of



FIG 2 Photomicrograph of the normal cutaneous glomus Near the top at the left is the afferent artery with its smooth muscle wall The contorted Sucquet Hoyer canal has been cut at various angles The thick wall and the numerous nuclei of the glomus cells are shown The preglomic nerve trunk is seen at the bottom of the illustration

specialization involving loss of myofibrils and assumption of rounded contour as well as development of an abundant nerve supply from periglomic nerve trunks the fibers of which terminate by nerve endings about individual glomus cells This nerve supply is perhaps independent of that of the remainder of the cutaneous vascular system

There is much experimental evidence to indicate the importance of the glomus in the thermal regulatory mechanism[6 7 8] Of interest is the fact that cutaneous glomus structures have been found in all warm blooded animals studied thus far while none have been demonstrated in cold blooded animal

will be given The normal cutaneous glomus is an arterio-venous shunt in the lowest layer of the corium (Fig 1) While this type of anastomosis is distributed on all surfaces of the hands and feet, it is most numerous in the nail beds The skin of the thorax and abdomen contains none The glomus is

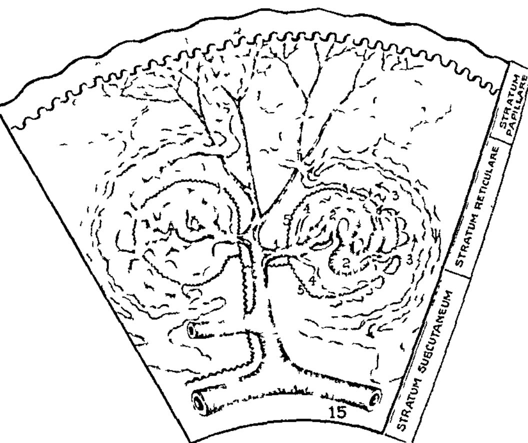


Fig 1 Diagram of the cutaneous glomus (1) Afferent artery (2) Sucquet Hoyer canal or arterio-venous anastomosis (3) primary collecting vein (4) preglomic arteriole (5) nerves. The arrows indicate the direction of blood flow (Reproduced from Popoff[14] throu h the courtesy of the author and the *Archives of Pathology*)

encountered in large numbers in the ears of certain mammals but has not been satisfactorily demonstrated in human ears There appears to be considerable variation in its distribution in various species The shunt permits a large amount of blood to flow through the part by providing an accessory circulation in addition to that of the capillaries of the skin

The cutaneous glomus possesses a structure differing from that of the remainder of the vascular system in the character of the cells in its wall and

Histology of Tumors of the Cutaneous Glomus

Certain small tumors of the extremities have their histogenesis in the cutaneous glomus They are composed of vessels with various sized lumina in no definite arrangement (Fig 3) Beneath their single endothelial layer the large clear, glomus cells are seen (Fig 4) It is the presence of these cells



Fig 4 High power photomicrograph of glomus cells to show their general appearance and their relation to the lumen of a small blood vessel

which makes it possible to establish the exact histogenesis of such tumors Not all of the cells are fully differentiated Some of them are elongate and present a few myofibrils while others retain the usual form of smooth muscle cells Between the cells there is found a homogeneous material staining as collagen by various histological methods but without its fibrillar structure In this material there are isolated glomus cells as well as nerve trunks and typical collagen fibers Nerve trunks are very numerous throughout the tumors There are large trunks which *enter* the tumors from the periphery branch and ramify among the glomus cells terminating among them by specialized nerve

The glomus dilates readily in response to cooling the extremity or the whole body The response to cooling and rewarming is greater and more prompt in the glomus than in other cutaneous vessels The glomus also dilates when heat is applied but the reaction does not come on until the elevation of temperature has resulted in considerable dilatation of other cutaneous vessels The glomus responds to pressure near it by dilatation whether the nerve supply is intact or not

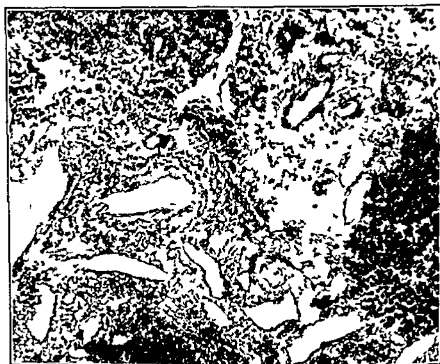


Fig 3 Low power photomicrograph of a glomangioma There are many vascular lumina The glomus cells often make large masses but are separated from one another by homogeneous material in several portions of the field

Application of acetylcholine or histamine produces dilatation of the cutaneous glomus while the action of adrenalin is to constrict it These responses are independent of the nervous system The response of the glomus to faradic stimulation of the autonomic nerves is dilatation This is more prompt and occurs in response to a smaller amount of current than the corresponding changes in the afferent artery of the glomus[6] In summary, the glomus behaves as an arterio-venous shunt which responds to a variety of stimuli with a promptness and delicacy not possessed by other blood vessels of the skin

for after removal and section of the tissue a large amount of blood escapes leaving grayish tissue

It is the association of such nodules with a particular group of *symptoms* which makes them clinically distinct The most constant and striking of these symptoms is pain The pain is very severe and in the descriptions of our patients it exceeds that due to any other cause in their experience It is not continuous but occurs in paroxysms which last a few minutes and are followed by respite The pain is lancinating and stabbing in character and is accompanied by a peculiar sickening sensation which has been compared to that

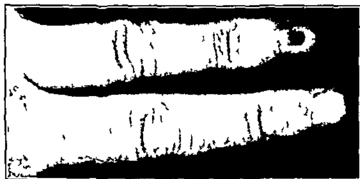


Fig 5 A subungual gl mangioma of the ring finger The lesion is sharply circumscribed There is no erosion of the overlying nail

produced by torsion of the testis or application of a hot iron It may remain localized In other patients or in response to greater stimuli the pain radiates up the extremity and to adjacent portions of the pelvis shoulder girdle or neck Many patients have lived in constant fear of the pain and have developed curious habits designed originally to protect the tumors These include such things as keeping the hand in the trousers pocket to prevent contact between clothing and a tumor on the thigh or the avoiding of crowds in fear of accidental pressure upon the lesion

Pain may be brought about by various sorts of stimuli The most effective of these are tactile in the usual case Slight touch applied to the tumor excites at once exquisite pain Thermal changes may initiate paroxysms of pain entirely similar in character and distribution to those resulting from pressure on the lesion In this respect cold is much more important than heat In fact the pain has been relieved in certain patients by immersing the affected extremity in water heated slightly above room temperatures The change in temperature may result in pain when applied to the whole body or to the region of the tumor Several patients have stated that seizures of great severity come on when they go outdoors in the winter Any local application of cold

endings The periphery is very sharply limited by compressed fibers of the adjacent corium The tumors thus represent organoid overgrowths of all elements of the cutaneous glomus Hence they are a special type of angioma, we prefer to call them glomangiomas for this reason

Clinical Manifestations of Glomangiomas

When first described, tumors of the cutaneous glomus were considered rare but at the present time over 100 instances have been described in the literature Many tumors with similar histology and clinical behavior were recorded in earlier papers under a variety of names With increased accuracy in diagnosis the condition is becoming recognized as an unusual one but by no means a curiosity

The tumors have been encountered at age periods varying from early childhood to senility The majority, however, are seen in middle life Within the limits of statistical error there is no predilection for either sex They appear to occur somewhat more frequently among Jews than in other races[15] There is much to indicate that glomangiomas are seen most often in patients of excitable temperament with labile autonomic mechanism

In location glomangiomas are found on the extremities or adjacent portions of the shoulder girdle They are encountered most frequently in the nail bed approximately 30 per cent of all recorded cases while others are found elsewhere on the hands and feet as well as on the arms, legs and thighs In one instance the tumor has been located on the acromion and in another on the chest wall near the axilla No glomangiomas have been described elsewhere on the thorax or upon the abdomen It is thus apparent that glomangiomas tend in general to follow the normal cutaneous glomus in location However in regions such as the thigh and upper arm, the glomic anastomoses have not been demonstrated satisfactorily in normal skin It may be that the structures are present but very rare in these places thus escaping microscopical detection, or that the tumors have developed from heterotopias The tumors have occurred singly except in one of Adair s patients[1] who presented three such lesions

The appearance of glomangiomas is less striking than the symptoms to which they give rise They are always small, usually from 5 to 8 mm in diameter In the nail bed they resemble dark red or purple blotches covered by intact nail (Fig 5) The area of discoloration is sharply circumscribed The nail bed is not eroded with increase in size of the tumor though the underlying bone may be Elsewhere glomangiomas appear as discrete nodules covered by a thin layer of intact skin (Fig 6) The color varies from red to purple and at times to a deep blue The color is due to the blood content,

Glomangiomas are also associated in a few instances with various disturbances of autonomic function at some distance from the tumors In a patient described by Paulian and his associates[13] the skin temperature of the extremity bearing the subungual tumor was higher than that of the opposite arm A patient recently seen at this clinic presented a glomangioma just beneath the surface of the skin covering the Achilles tendon (Fig 6) The skin temperature of that leg was 1° C higher than that of the opposite extremity After surgical removal of the tumor the skin temperature was the same in each leg Perhaps the most unexpected manifestation of distant autonomic influence so far recorded is to be found in the case of Barre[4] whose patient suffered from a Horner s syndrome which disappeared after removal of a subungual glomangioma

In view of such accompaniments of inconspicuous lesions much speculation has been put forward to link even convulsive seizures with the tumors To establish any such relationship these findings must disappear after removal of the tumor Furthermore if the manifestations are those frequently encountered in hysteria the elements of suggestion and the general nervous tension due to the paroxysms of pain must be taken into consideration Relief from pain thus may result in cure of symptoms which are not necessarily connected with the glomangioma by direct neuronal pathways

In view of the severity of the pain associated with tumors of the cutaneous glomus it is surprising that many years elapse between the onset of symptoms and the appearance of the patient at the clinic With few exceptions the interval is five years or longer The average duration of symptoms when the patient was first seen was fourteen years in a series of 65 cases collected from the literature in 1935 One patient had had symptoms for forty years

In about 40 per cent of patients with glomangiomas there is a history of a single severe trauma followed after an interval by the appearance of the tumor One of the patients in this clinic received a blow to the upper arm This was followed by a reddish spot which gradually changed color to greenish yellow to blue as time went on The tenderness of the area never entirely disappeared After several months the region became acutely painful By that time the patient presented a glomangioma of typical appearance and responses In another patient the tumor developed at the place where the patient had been bitten by a horse The history of such antecedents is too frequent and too definite to be disregarded

The *clinical diagnosis* of glomangiomas is easily made if the possibility of such a lesion is kept in mind Of especial value in differential diagnosis are the radiating character of the pain the response to cold the frequency of subungual location the long duration of symptoms and the history of previous severe trauma to the site of the lesion Malignant melanoma occurs beneath

objects to the site of the tumor usually results in so much pain that the procedure has to be abandoned at once The degree of responsiveness of the tumors to thermal changes varies considerably from patient to patient It is present to some degree, however, in nearly every instance In occasional cases pain may be brought on also by strenuous exercise of the extremity bearing the tumor Not many patients describe this experience, but in a few the attacks brought on in this way are sufficiently annoying to interfere with their work



FIG 6 A glomangioma over the Achilles tendon Note the elevation of the skin without ulceration

It is thus evident that the various factors resulting in paroxysms of pain are those which cause dilatation of glomic vessels There is some collateral evidence to support such a view in the fact that a few patients have noticed that their tumors become larger and deeper in color during the seizures The difference between the activity of normal glomic vessels and those of the tumors is quantitative The tumors respond to stimuli so small that they do not affect the normal glomus and to larger stimuli they react with pain Maximal stimuli applied to the normal glomus also result in painful responses as in immersing the finger tips in ice water for several minutes Glomangiomas therefore represent functional as well as morphological overgrowths of the cutaneous glomus

In some instances attacks of pain may be apparently spontaneous The longer the patients are studied and the more thoroughly stimuli are sought the less often spontaneous seizures are found Yet there remain instances when the initiating influence has not been discovered

Prognosis

The prognosis in glomangiomas is good. A few instances of recurrence have been described[15] but these are distinctly uncommon. The recurrences are as amenable to surgical removal as the original lesions. No instance of malignancy or extensive local invasion has been recorded. Furthermore all symptoms are relieved promptly by surgical removal. From the time of operation the paroxysms of lancinating pain do not occur again. The wound heals with no more pain or tenderness than one made for removal of any other cutaneous lesion. Differences in cutaneous temperature, even the Horner's syndrome in Barré's case[4], have disappeared after removal of the tumors. The severity of the pain, its long duration and the seriousness of lesions with which the condition has been confused in contrast to its easy and permanent cure give the glomangioma an especial interest among the various types of subcutaneous nodules.

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the nail bed where it may simulate the appearance of a glomangioma but the characteristic pain and thermal response of the glomangioma are lacking The radiating pains sometimes associated with neurofibromas can not be elicited by thermal stimuli

The possibility of a tumor of the cutaneous glomus should be kept in mind in the study of patients with obscure painful conditions of the extremities A few patients with such symptoms have never recognized that there was an exciting point for the production of their pain Many have been treated for psychoneurosis for years Some have been thought to have spinal cord tumors Neuralgia has been an especially common diagnosis Barre called particular attention to this association in his original communications[3,4] A meticulous search of the affected extremity for glomangiomas may contribute much toward an understanding of the illnesses of such patients

Treatment

The only satisfactory treatment for glomangiomas is surgical excision Novocaine anesthesia is very satisfactory when induced as a nerve block Infiltration of the tumor and its surrounding tissues with novocaine however does not always give complete anesthesia until one has used a considerably larger amount than would be required for other cutaneous lesions The tumor itself may continue to be painful after anesthesia has been secured in the surrounding tissues Glomangiomas located beneath the skin may be excised with a narrow margin

When the tumor is located beneath the nail the nail must be removed partially It is taken from the nail bed to a point slightly below the tumor, the base of the nail is preserved Then the tumor may be excised without difficulty After this type of removal the nail grows again in normal contour Excision of smaller portions of nail is likely to result in distortion which may be more or less permanent Tumors situated near the lateral border of the nail bed have been removed by excision of nail and matrix by the method used for ingrown toenails The first procedure is to be preferred in nearly all instances The circumscribed character of glomangiomas allows removal with a narrow margin of adjacent normal tissues a consideration of importance in dealing with subungual tumors More radical operative procedures, including amputation of digits are entirely unnecessary

Treatment with radium has been tried in one instance[1] Seven hundred mc hr of radium were applied to a subcutaneous glomangioma without any appreciable effect In view of the simplicity of surgical removal and its very satisfactory results it appears that irradiation of any type has no place in the treatment of these lesions

CHAPTER XIV-E

ESSENTIAL AND ORTHOSTATIC HYPOTENSION*

By FREDERICK R TAYLOR

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ESSENTIAL HYPOTENSION

ORTHOSTATIC HYPOTENSION

ESSENTIAL HYPOTENSION

Synonyms — Chronic idiopathic hypotension simple hypotension constitutional hypotension primary low arterial tension

INTRODUCTION

Essential hypotension may be defined as a condition in which there is a persistently low level of the systolic blood pressure without discoverable

* For discussion of hypertension see Chapter XI Vol III

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Etiology and Pathogenesis

The etiology of essential hypotension is unknown It is generally accepted that a lack of the normal vasomotor tone plays a large part in the condition but just how this lack is brought about is not clear It seems probable that some imbalance in the vegetative nervous system must exist but again we are ignorant of how this comes about Evidence is accumulating to the effect that certain brain centers have a regulatory effect on blood pressure but no proof of a cerebral etiology of essential hypotension has been produced thus far Rogers[1] has shown that removal of the cerebral hemispheres in the pigeon leaving the thalamus intact and body temperature normal leads to a constant fall in arterial pressure of from ten to twenty per cent This fall comes on immediately and lasts as long as 75 days after operation Removal of the hemispheres and thalamus causes a loss of temperature regulation and usually leads to a slightly greater fall in arterial pressure than does loss of the hemispheres alone The experiments of van Bogaert[13] suggest the possibility of a disturbance of a special brain center being at fault Having shown previously that he could produce a considerable arterial hyper tension by stimulating electrically or chemically the retrohypophyseal portion of the floor of the 3rd ventricle he searched for a similar area the excitation of which would cause a marked fall of arterial pressure He found such an area at the foot of the vascular pedicle formed by the division of the internal carotid into its branches giving rise to the hexagon of Willis or in other words at the junction of the floor of the 3rd ventricle with the horn of Ammon Stimulation of this area produced prolonged hypotension of considerable degree Van Bogaert concludes as follows There exist then at the base of the brain in the floor of the 3rd ventricle two definite physiologic points the excitation of one of which causes hypertension and of the other hypotension the latter resulting from inhibition of the bulbar pressor tonus The proximity of the two regions often causes mixed symptoms in experimental work The relation of this experimental work to the clinical syndrome seems very remote

In many cases certain associated findings have been considered contributory etiological factors such as a ptotic build with poor abdominal musculature giving inadequate support to the splanchnic vessels but essential hypotension may occur in persons of athletic build Many years ago Cannon[14] showed that the normal systolic pressure is much greater than usually is necessary to carry on the circulation adequately This extra pressure is needed whenever the arterioles of any organ or small area relax in order to prevent other regions from being seriously

cause This excludes hypotension due to such factors as Addison's disease pulmonary tuberculosis influenza and certain other fevers chronic myocardial failure etc Contrary to the facts observed in essential hypertension in which the level of the diastolic pressure is of major importance in hypotension it seems to be of little or no significance Just as diastolic hypertension means a constant strain on the circulation so systolic hypotension severe enough to cause symptoms means a constant inadequacy of the circulation

Authorities are not in uniform agreement as to the minimum level of systolic pressure which is to be considered normal in the adult White[1] says that hypotension is attended by a systolic pressure below 90 mm of mercury in an adult or by a marked fall from a previous hypertensive level even though the figure at the time of examination is within the usual normal limits Riesman defines low blood pressure in an adult as a systolic pressure under 100 mm Hg Meyer[3] differentiates between the sexes using 105 mm Hg as the upper systolic level of hypotension in the adult male and 100 mm in the adult female Most writers however accept a systolic pressure of 110 or below as evidence of hypotension in an adult of either sex and this will be the criterion accepted in this chapter

History

From 1733 when Stephen Hales observed the arterial pressure of a horse by inserting a long glass tube into an artery of that animal up to the dawn of the 20th century blood pressure studies were limited largely to the work of the experimental physiologists though clinical inspection and palpation of the superficial arteries in man gave evidence of severe grades of hypertension Even when the sphygmomanometer came into routine clinical use about the beginning of this century the attention of clinicians was focused almost exclusively upon hypertensive states because of their dangerous potentialities and with a few notable exceptions little appeared in the literature on hypotension until about 1910 Since then a large number of contributions have appeared on the subject

One of the earliest writers on essential hypotension in the United States if not the earliest was Louis Faugeres Bishop Sr who published several articles on it from 1904 to 1907[4 5 6 7 8] In 1910 Edgecombe of London[9] published a very valuable detailed series of observations on the condition as observed in himself over a period of two years In 1927 Roberts of Atlanta[10] made an important clinical study of hypotension In 1927 Lian and Blondell[11] gave a brilliant contribution to the French literature on the subject

relation to the pulse volume With a weak pulse they may be weak or vigorous Some patients complain that they have had a weak heart and pulse all their lives The systolic pressure may vary in different subjects from 110 mm Hg down to 80 mm but almost never below that figure in an adult except during a syncopal attack Central systolic levels from 95 to 110 are much more frequent than levels below 95 The diastolic pressure and thus the pulse pressure varies within rather wide limits and seems of little or no clinical significance Authorities are generally agreed that no particular diastolic level sets off essential hypotension from normal arterial pressure and that the systolic level is the sole criterion

Edgecombe[9] has given us the most intensive study of a case of essential hypotension in the literature made on himself He took systolic blood pressure readings twice daily or oftener for a period of two years under varying conditions In 200 consecutive days he found his average morning pressure to be 94 1 mm Hg and his average evening pressure 104 9 mm showing an average daily rise of 10 8 mm His maximum morning systolic pressure was 110 his minimum 80 His maximum evening reading was 120 and minimum 85 He attributed the usual diurnal rise to increased heart action brought about by various stimuli applied during the day and not primarily to increased peripheral resistance for he found that his vasomotor tone as measured by the relation between the venous and arterial pressures was higher early in the day than in the evening The usual sequence of events was as follows a rise in pressure of about 6 mm after getting up out of bed a further rise after breakfast partly due to food and liquid ingested but mainly dependent on whether tea or coffee was taken the rise being about 7 mm after coffee Smoking after breakfast caused a further rise of about 8 mm The level of pressure reached after breakfast was maintained with varying oscillations until evening so the diurnal rise occurred relatively early in the morning If neither tea coffee nor tobacco were used the rise after breakfast amounted to only 2 or 3 mm and this was maintained throughout the day provided there were no further sources of cardiac stimulation Exercise increased the daily rise in proportion to its severity the average rise on days without special exercise being 9 2 mm while that on days with moderate exercise was 11 6 mm and that on days with more severe exercise 13 5 mm The immediate effect of exercise was a rise followed shortly after cessation of the exercise by a fall but this in turn was followed by a secondary rise in pressure Hard mental work caused an average rise of 17 6 mm and worry and excitement had a similar effect Altitude was found to have a

drained of blood It seems clear that essential hypotension is not dependent solely or chiefly on any local vascular condition but rather on factors affecting the entire arterial tree Lian and Blondell[11] believe that a simultaneous cardiac and vascular disturbance exists based on an endocrine sympathetic disturbance Dearborn[1] notes that a disturbance of the posterior pituitary often has been suspected McCrae[16] believed that the capillaries often are at fault though how he did not know Others have suggested that a histamine like poison may be elaborated in the body and cause capillary injury

Symptomatology and Physical Findings

Low blood pressure if not of extreme degree may be compatible with perfect health and show no symptoms In a series of 13 cases recently studied by the writer 5 failed to show symptoms which he could attribute to the hypotension The lower the pressure the more likely are symptoms to develop The majority of asymptomatic cases are in those with a systolic pressure of over 100 mm Hg It is unusual to find a total lack of symptoms when the pressure is below that level though such cases have been observed Dearborn[1] reports such a case in a 44 year old physician who was a physical director

The most frequent symptom complained of is general asthenia Another very common symptom is dizziness which in severe cases may go on to actual syncopal attacks These may be brought on by emotional stress or may occur without obvious immediate cause Prolonged standing may bring on fainting too though this is more frequent in the orthostatic cases to be described later Susceptibility to cold with a tendency to develop cold numb cyanotic extremities is noted often As stated above a ptotic asthenic habitus often is associated with essential hypotension but is by no means a necessary part of the picture Other frequent symptoms are physical and mental fatigue emotional depression constipation acne and certain other skin disorders functional nervous disturbances frequent colds or chronic catarrhal states palpitation and headache Fisher[17] notes that many hypotensives adjust poorly to emergencies Holt[18] adds to the above list of symptoms gaseous distention of the abdomen menstrual irregularities backache insomnia etc and remarks that the number of symptoms seems limited only by the number of questions asked She does not however believe that all such symptoms are directly attributable to the hypotension but interprets them rather as evidence of an associated psychoneurotic state

The cardiac impulse and sounds vary greatly and bear no constant

tachycardia may accompany essential hypotension They stress brady cardia and vagotonia in general as more characteristic

The average level of blood pressure in Orientals is lower than in Occidentals Most authorities find a lowering in the blood pressure of American civilians after prolonged residence in the Orient Soldiers however do not seem to exhibit this phenomenon perhaps because of their more active life Tung points out that the lowering is not a tropical effect due to sweating or peripheral vascular dilatation as he noted such lowering in Peking the climate of which is neither tropical nor subtropical The general slowing of the tempo of life in the Orient may be the explanation

R F Weiss[3] notes with regard to mental disease that hypotensives seem to have schizoid tendencies whereas hypertensives have cyclothymic tendencies

Diagnosis

This depends on two factors first on establishing by repeated blood pressure observations using both arms in old people and others with arteriosclerosis or other conditions which tend towards inequality of the pressure on the two sides the fact that a more or less constant systolic level of 110 mm Hg or less exists and second on excluding other con ditions to which chronic hypotension may be secondary such as Addison s disease pulmonary and other forms of tuberculosis myxedema severe anemias of all types chronic myocardial failure from any cause (cardiac infarction is especially important to exclude) and advanced cachectic states Johnson[24] notes that the habitual use of certain coal tar drugs may cause chronic hypotension and also mentions the increase in the condition since the influenza pandemics of 1918 and 1920 Chronic myocardial failure often shows a relatively high diastolic pressure when the systolic level is low but in essential hypotension the diastolic level is so variable that this point is at best of only relative significance

Prognosis

The prognosis as to life expectancy is excellent often better than that of normal individuals As a class patients with essential hypotension are noted for longevity Friedlander who has given perhaps the most exhaustive discussion of hypotension of all types quotes Fisher to the effect that in 3 389 persons aged 16 to 60 accepted for insurance by the Northwestern Mutual Life Insurance Company with systolic pressures of

definite effect in raising his blood pressure His average morning reading during 29 days in Switzerland at an altitude of 6 000 ft was 10 8 mm above his average morning reading in England for the 29 days immediately preceding 10 mm was the average rise of his evening pressure as compared with that in England The rise became evident the evening of his arrival in Switzerland so is not attributable to exercise The increased oxygen demand at the higher altitude with consequent increase in heart action seemed to explain the rise for the most part though certain other factors may have been operative such as a lower atmospheric temperature with consequent tendency to peripheral vasoconstriction Constipation lessened the daily rise in pressure but aperients did not show this effect Edgecombe believed that they might remove some depressor substance The Vichy douche aerated Nauheim baths at or below 90° F and needle baths graduated from warm down to cool or cold raised his pressure but he cautioned against such procedures in those with a poor peripheral circulation who react unfavorably to them

A point of considerable importance as emphasized by Bowes[19] was that in the aged and others with advanced arteriosclerosis there is often a marked difference in the blood pressure of the two arms and it is advisable in such cases to take the pressure in both arms before concluding that a general hypotension exists Such difference too is common in those with normal arteries

Roberts[10] finds that hypotension seems to be distributed equally among the sexes and makes the interesting observation that hypotensive patients have proportionately more normal hearts than do those with normal blood pressure or hypertension He believes that women tend to develop hypotension at an earlier age than men He finds that focal infections are common accompaniments of hypotension but as they are so frequent in general this would seem to indicate little He notes that in sick adult negroes hypotension is more frequent than hypertension He agrees with John Phillips that influenza often is followed by prolonged hypotension and quotes Rolleston to the effect that the toxins of influenza may damage the adrenals Some years ago however Christian in a personal communication remarked that adrenal damage due to influenza is difficult of proof as manipulation at autopsy so often gives the appearance of pathological change in the adrenals

Garvin[9] gives an interesting report of 6 cases of essential hypotension in one family their systolic pressures ranging from 94 to 108 All were in excellent health active and vigorous most were robust and hypersthenic one was obese Meakins[1] also recognizes a hereditary or congenital factor Lian and Blondell[11] note that either bradycardia or

culation In patients showing extreme weakness and a white line tache McCrae[16] advised epinephrine therapy He cites the case of one patient who recovered in three months on epinephrine by mouth starting with 5 drops of a 1 1000 solution thrice daily after meals and gradually increasing to 10 drops at the same intervals At the time of McCrae s report the patient had remained well for over a year after this treatment had been discontinued If the view generally accepted by physicians and pharmacologists be true however epinephrine is rarely effective by mouth but must be given parenterally In general the effect of epinephrine given subcutaneously or intravenously is too fleeting to be of great value in so constant a condition as essential hypotension It is often of definite value however in temporary emergencies such as syncopal attacks Ephedrine has a more prolonged effect and is preferable for ordinary use It may be given in 30 mgm (gr ½) doses in the early morning and at midday Its use at night may cause insomnia

Joachim[6] advises small doses of strychnine continued over a considerable period with caffeine pituitrin or additional strychnine in emergencies The present writer however has never found strychnine of the slightest use in an emergency Lian and Blondell[11] suggest strychnine ergotin and oxygen in addition to a full diet but admit that it is as difficult to raise a persistent hypotension permanently as to lower a similar hypertension in like manner Pierach[77] notes that many hypotensives are great coffee drinkers and that this definitely helps them This has been true also in the present writer s experience

Storz and Kirk[79] are enthusiastic about benzedrine called eupho dyn in Germany They find that in 14 cases a dose of 20 mgm (gr ⅓) would cause the blood pressure to rise reaching its maximum level in 2 hours and holding up from 5 to 8 hours Benzedrine sulphate is the preparation usually employed by mouth in America and may be given in doses of 20 mgm (gr ⅓) on arising and 10 mgm (gr ⅙) at midday It is well to avoid its use at night if possible as it like ephedrine may cause insomnia If these two drugs prove helpful but cause nervousness small doses of phenobarbital or some other sedative may be combined with them

ORTHOSTATIC HYPOTENSION

Synonym — Postural hypotension

Definition — A chronic state characterized by persistent failure of the regulatory mechanism whereby in normal persons the blood pressure is kept relatively constant regardless of the position of the body In this

100 mm or less the mortality was 35 per cent of the expected mortality whereas the company's general mortality experience is about 80 per cent of the expected rate Fisher of Australia[17] remarks concerning hypotensives with symptoms that they live miserably but they live long and the arteriosclerosis of advancing years helps them Hypotensives are easily shocked by trauma hemorrhage etc Riesman states that in adults with a systolic pressure under 100 mm Hg the margin of safety possessed by the circulation is small and a grave operation unless extra precautions are taken must end disastrously Sudden death in a syncopal attack in the absence of shock is very rare

Treatment

Obviously in those hypotensives who are devoid of symptoms no treatment is required The measures employed should depend to some degree on the severity of the symptoms and the favorable or unfavorable reaction to certain procedures A full diet generally is indicated Obvious foci of infection should be removed on general principles and some patients will be helped thereby In the less severe cases hard work physical and mental may be beneficial In the more severe cases however the patients are too weak to benefit by this and are only exhausted further by it Heavy exercise should never be kept up if it causes prolonged fatigue Moderate exercise especially of the abdominal muscles may be helpful in some cases Cold baths may be of benefit to a few patients but many hypotensives react poorly to them and the end result is a chilly weak depressed feeling with cold cyanotic extremities and general pallor of the skin Daily contrast baths often are helpful these consisting of alternating hot and cool rarely cold baths of only a few moments duration each The shower or needle bath is adapted best for this procedure as the temperature can be changed from hot to cool and vice versa with any degree of rapidity desired The patient often will find the best technic by trial and error Bishop[7] advises very hot baths of short duration for children with hypotension When the patient can afford it removal to a high altitude may be beneficial The consequent rise in blood pressure may make exercises beneficial that were previously exhausting and this may improve the general muscular tone and bodily vigor so as to give lasting benefit even after returning to a lower altitude More satisfactory results however are likely to be obtained by a permanent change of residence to the high altitude when this is practicable

Some asthenic hypotensives with very lax abdominal walls may be helped by an abdominal pad and binder to support the splanchnic cir

Pathological Physiology

Bradbury and Eggleston[31] note that in their three cases both the cardiac accelerator and augmentor functions of the sympathetic could be stimulated by epinephrine but such stimulation did not restore the capacity to maintain the blood pressure level in the face of the influence of gravity They found the responsiveness of the vasoconstrictor endings of the sympathetic to stimulation by epinephrine much impaired or entirely lost They also note that the inability to sweat common to all three patients was not due to defective sweat glands or lack in their ability to respond to pharmacological stimulation of the sympathetic endings neither could it be attributed to the low blood pressure They conclude that paralysis of the vasoconstrictor endings seems the only reasonably adequate explanation of the blood pressure reactions met with in these cases

Barker[33] finds a hypofunction of certain parts of the sympathetic nervous system as evidenced by loss of the reflex postural or orthostatic vaso constriction necessary to maintain blood pressure against the force of gravity by hypohidrosis or anhidrosis in advanced cases and by the loss of reflex acceleration of the cardiac rate He notes that the failure of atropine to affect the heart rate means that while the vagus function is inhibited by the drug the accelerator nerves are not working He found that epinephrine and ephedrine caused some vasoconstriction and cardiac acceleration by direct stimulation and that pilocarpine usually would cause sweating in dry areas He notes that cases with unilateral anhidrosis have been reported suggesting some focal abnormality of the nervous system He concludes that the disturbance probably is in the sympathetic nervous system and peripheral in most cases and does not concern the myoneural structures primarily

The persistence of the condition in most cases suggests an organic basis though certain cases which recover suggest transient functional syndromes Alvarez and Roth[34] found that tourniquets around the thighs of their patient prevented dizziness when the pressure fell This patient showed very little ability to sweat in the electric cabinet but more in response to pilocarpine Inhalation for five minutes of a mixture consisting of 10 per cent carbon dioxide and 90 per cent oxygen followed by placing an arm in ice water caused her pressure to rise from 100/65 to 120/80 showing that the vasometer system was functioning well Alvarez and Roth believe that there is often a splotchy injury to the nerves affecting the sweat glands and often injury to the cardiac accelerator mechanism

state both the systolic and diastolic pressures in the arms are significantly lower in the erect posture than when the body is horizontal and tend to reach their maximal levels when the body is in an inverted or semi inverted position with the head low and the feet high

History

According to Korns and Randall[9] the first inklings of this condition in the literature are found in C Laubry s brief mention of a case[30], which was referred to him in 1891 by Babinski who accidentally discovered that the patient s blood pressure was low and sent him to Laubry who demonstrated the orthostatic nature of the condition In 1925 Bradbury and Eggleston[31] published the first detailed study of orthostatic hypo tension known to the writer describing three cases Several other reports have appeared since then

Etiology and Pathogenesis

The actual etiology is unknown Bradbury and Eggleston[31] note that there is an almost total loss of peripheral vascular tone and of the mechan ism by which the blood pressure is maintained in different positions of the body They state that there seems to be an extensive and peculiar disturbance in the functional activity of the vegetative nervous system They found evidence that the sympathetic accelerator control of the heart was impaired in their cases as neither atropine nor a pronounced fall in blood pressure increased the heart rate They noted in addition that the responsiveness of the vagus to a pronounced elevation of blood pressure brought about by the recumbent posture and epinephrine seemed largely wanting

Pathological Anatomy

No definite characteristic structural changes have been found One of Bradbury and Eggleston s cases came to necropsy but unfortunately examination of the brain was not permitted They report[3] that supra renal disease and status lymphaticus were disproved in this case They believe that if there is any localized lesion in essential hypotension it will be found in the brain or spinal cord Their anatomical diagnosis in this case was chronic myocarditis acute dilatation of the heart atrophy of the prostate and chronic tuberculosis of the bronchial lymph nodes The lungs were negative

system at the time he felt something break loose in his abdomen Sanders[36] also cites another patient whose symptoms started on being blown up by a shell Most patients however do not date their trouble from any definite injury

Other frequent symptoms are cold blue numb extremities a feeling of abnormal heart action upper abdominal distress anhidrosis etc Ellis and Haynes[37] believe that the center controlling the postural reflex is in the brain rather than the cord

Riecher and Upjohn[38] note involuntary closing of the eyes and slight convulsive jerking of one arm often associated with sweating of the limb on assuming the erect posture and caution that such jerking might lead to a diagnosis of epilepsy especially if associated with syncope

A frequent finding is oliguria while in the erect posture with a normal or increased output of urine when recumbent C R Weiss[39] cites the case of a patient whose day output of urine was 430 c c and night output about 1200 c c Langston[40] has noted orthostatic nitrogen retention and decreased phthalein output when standing

The changes in blood pressure with changes in bodily position are diagnostic The following figures are taken from cases cited by Riecher and Upjohn[37] Laubry and Doumer[41] Allen and Magee[4] and Alvarez and Roth[34]

	mm Hg
Patient supine	140/70
Patient sitting	124/6-
Patient sitting after 3 minutes	70/50
Patient standing	38/25
Patient supine	140/72
Head dropped 60° (after 2 minutes)	170/82

Various patients

Recumbent	155/90	170/90	160/100	130/80	90/60	66/60
Seated	105/60	140/70				
Standing	95/50	110/60	110/60	120/80	syst 50	
Head down 90	138/100					
Head down 45°	135/90					
Recumbent	118/82					
Head up 45°	92/70					
Head up 90°	64/50?					
4 minutes later	44/24?					

Croll Duthie and MacWilliam[43] cite a unique case in a 37 year old policeman His supine pressure was found to be 135/90 but a few days

Symptomatology and Diagnosis

The most characteristic symptom consists of dizziness or faintness on assuming the erect posture This may develop into actual syncope if the patient does not assume the horizontal posture promptly which experience usually teaches him to do (Other discussion of the syncope of postural hypotension will be found in Chapt VIII–A Vol II of Oxford Medicine) In the worst cases even sitting upright in a chair may cause these symptoms Sanders[35] has described such a case His report is the most interesting one the present writer has discovered in the literature on the subject exhibiting a considerable variety of symptoms and giving cause for speculation as to etiology As reports of orthostatic hypotension are relatively rare less than 30 being known to the author to date a brief resume of the case will be given The patient a 34 year old lawyer complained of dizziness faintness and mental haziness on prolonged standing In addition he had chronic edema of his feet and legs and two or three watery stools daily When 21 years old while weak and fatigued from a severe cough he took a long hike as a soldier under heavy equipment On running up a hill he felt as if something had broken loose in his abdomen He had a constant dragging feeling in his abdomen and never regained full strength after this After returning to duty he developed a severe diarrhea but kept at work While in this condition he jumped from a truck to the ground and felt as if his abdominal organs were sinking and had pain and a queer feeling in his sacroiliac region hips and legs He also felt faint but did not lose consciousness He had a similar attack later on jumping from a truck again and thought he lost consciousness a few moments this time After that he was subject to frequent faintness and dizziness on standing The diarrhea continued for years his stools being repeatedly negative for parasites He was forced to do most of his work as an attorney lying prone with two or three cushions under his abdomen His mind was clear in this position but became fogged on sitting or standing He had repeated falls due to faintness once fracturing his right femur It was noticed that his face was pale in these attacks His pulse rate varied between 40 and 60 lying down and from 60 to 70 sitting or standing Ocular pressure or pressure on the vagus nerve on either side of the neck caused no change in the pulse rate The patient while sitting with his arm at the side showed a blood pressure of 130/74 Raising his arm till the elbow was at the level of the upper thorax lowered his pressure to 110/68 Raising his arm still further so that the sphygmomanometer cuff was at the level of his head reduced the pressure to 84/60 Sanders assumes that he sustained a definite injury to his autonomic nervous

gested but Barker[33] points out that this may be inadequate and that 50 mgm (gr 3/4) of ephedrine sulphate three to five times daily may be required He notes however that ephedrine is of little use if advanced arteriosclerosis be present If it fails he suggests ergotamine tartrate hypodermically once or twice daily though he adds that there are some objections to this When hypohidrosis or anhidrosis is part of the picture he advises 13 mgm (gr 1/5) of pilocarpine by mouth as often as needed to cause normal sweating Often the patient s symptoms are worse in the early morning In such a case the dose should vary accordingly Allen and Magee[4] gave a patient 100 mgm (gr 1½) of ephedrine sulphate at 6 A M one hour before rising so he could dress and shave comfortably and then gave 50 mgm (gr 3/4) at 10 A M and at 1 4 and 7 P M The patient improved greatly but suffered from insomnia and barbiturates were required to control this Later an additional 50 mgm (gr 3/4) of ephedrine was added at 7 A M because the patient felt a little weak in the first part of the morning on the original schedule

C R Weiss s patient[39] had small doses 25 mgm (gr 3/8) of ephedrine sulphate every 3 hours giving 5 doses daily for six months During this period his weight increased from 112 to 156 lbs the blood pressure phenomena disappeared and he had remained well for 2 years after medication was stopped As this is the only cure reported in the literature the possibility of coincidental spontaneous recovery must be kept in mind

Davis and Shumway Davis[17] report two cases relieved by benzedrine sulphate One patient received 20 mgm (gr 1/3) a half hour before rising in the morning and 15 mgm (gr 1/4) at lunch time Later two 10 mgm (gr 1/6) tablets were added at 4 P M The other patient was given 25 mgm (gr 3/8) before rising and 15 mgm (gr 1/4) at lunch but the morning dose had to be increased to 40 mgm (gr 2/3) and 15 mgm (gr 1/4) added at 4 P M

Korns and Randall s patient[30] was helped by both ephedrine and benzedrine sulphate but preferred the latter because it made him less tremulous and caused less insomnia than did ephedrine and seemed slightly more effective in dispelling weakness The dosage of the two drugs found effective was ephedrine 48 mgm (gr 3/4) every two hours from 6 A M to 6 P M inclusive benzedrine sulphate 40 mgm (gr 2/3) at 6 A M 30 mgm (gr ½) at 8 A M 20 mgm (gr 1/3) at 10 A M 12 M and 2 P M and 10 mgm (gr 1/6) at 4 and 6 P M With these large doses severe insomnia resulted from either drug and full doses of barbiturates were only partially successful in overcoming it This patient like many others felt worse in warm weather He did not sweat in response to pilocarpine

later it had risen without obvious cause to 240/140 at which time his pressure sitting was 160/100 and standing 100/70

The effect of Addison s disease in producing constant hypotension is of course a medical commonplace but Duggan and Barr[44] have reported an extraordinary case of postural hypotension complicating Addison s disease in a negro Their blood pressure findings were as follows horizontal 98/64 head down 80° from horizontal 86/64 feet down 60° from horizontal neither blood pressure nor pulse obtainable

Very recently MacLean and Horton[4] have reported a case of myasthenia gravis with postural hypotension The ability to sweat was absent throughout both lower extremities and the left upper extremity Their studies led them to believe that the autonomic nervous system was intact and they raise a question of the possibility of the postural hypotension in this case being due to a failure of the chemical mediation of nerve impulses in smooth muscle They advise that myasthenic patients be investigated for evidences of smooth muscle derangement and that patients with postural hypotension be studied for myasthenic characteristics

Arnovljevic and Milanovitch[46] believe that orthostatic hypotension is more frequent than reports would indicate and that many cases would be discovered if the routine practice were adopted of taking blood pressure both sitting and recumbent They suggest that some with normal blood pressure in the sitting posture would show hypertension when recumbent because of a relative orthostatic hypotension

Prognosis

So far as is known the condition is not fatal per se In some cases it may decrease or even disappear spontaneously but this is not the rule C R Weiss[39] reports what he considers a cure which will be discussed in the next section

Treatment

Rest exercise and hydrotherapy have proved useless in this condition A few patients have been helped by an abdominal binder but this is exceptional Many drugs have been tried and found wanting Two appear to be useful in most cases viz preparations of ephedrine and of benzyl methyl carbinamine (benzedrine) Ephedrine has been in use longer and is recommended by most writers The dose should vary with the individual case 25 mgm (gr 3/8) several times daily has been us

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While writing this chapter Korns, in a personal communication has informed the author that he has also used a new drug paredrine alone and in conjunction with benzedrine sulphate in the treatment of orthostatic hypotension and his findings are to be published soon in Annals of Internal Medicine Paredrine according to the manufacturers (Smith Kline and French Laboratories Philadelphia) is para hydroxyl benzyl methyl carbinamine

In all cases relieved by medication except the cure of Weiss the relief appeared to be due to a general raising of both systolic and diastolic pressures in all positions The variation of pressure in different positions persisted but occurred at higher levels so that the minimum pressure in the erect posture was not low enough to be disabling

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CHAPTER XIV-F

ARTERIAL HYPERTENSION

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primary change is an elevation of the blood pressure due to a functional generalized spasm of the arterioles with the cause of this constriction still completely unknown

History

Since the time of Bright[6] in 1827 the existence of human arterial hypertension was suspected by many clinicians but pulse tracings or palpation of the radial arteries were the only evidence to back up this suspicion Von Basch (1881) is credited with being the father of modern sphygmomanometry yet actually it was Riva Rocci (1896) who popularized clinical blood pressure determinations by the invention of a satisfactory sphygmomanometer It was his apparatus that had the first air pressure cuff which is now universally utilized

The present day understanding of essential hypertension began around 1900 when Allbutt[5] and later Huchard[7] clearly separated patients with arterial hypertension into two groups those who had renal involvement and those whom these investigators believed had what we now call primary arterial essential hypertension Clinicians prior to Allbutt and Huchard and even some of their contemporaries such as Mahomed[8] and von Basch had come close to the modern concept of essential hypertension but they persisted in the belief that nephritis and albuminuria would necessarily be the end of these early hypertensives All butt however clearly described in detail his extensive observations during the course of many years of patients with essential hypertension and clearly emphasized that these people did not necessarily develop renal disease and most commonly died of cerebral hemorrhage Allbutt applied the term hyperpiesia to this newly discovered group of cases and this term has remained popular in England The American term essential hypertension is derived from the German essentielle Hypertonie which was applied by Frank[9]

In the past ten years however the concept of arterial hypertension took a temporary swing back to the original idea that the etiology resided in a primary kidney disease This change was started by Goldblatt who showed experimentally in animals that arterial hypertension may be produced by a disturbance in the function of the kidneys even without demonstrable renal pathology or impaired renal function tests The possibility therefore that essential hypertension has a renal etiology must remain open at this time However it is fair to say that the animal work of Goldblatt has been completely unsubstantiated in human essential hypertension Finally it should be noted that the downward swing of the pendulum from Allbutt to Goldblatt seems to have about levelled out and the clinical impression is gaining ground that Goldblatt animal hypertension is distinctly different etiologically from human essential hypertension

INTRODUCTION

The accurate study of arterial hypertension naturally started with the invention of the modern blood pressure machine by von Basch in 1881[1] and the pneumatic compression cuff by Riva Rocci in 1896[2] The discovery of elevated readings of the blood pressure in some human beings resulted in the gradual separation of such cases into those associated with primary renal disease cases without renal disease, cases due to hormone production by certain tumors and to various intoxications In the present chapter it is planned primarily to describe those cases which have been most commonly called essential hypertension with a brief discussion of the differential diagnosis of the other causes of arterial hypertension

The definition of essential hypertension called hyperpiesia by the English and hypertonia by the Germans was relatively easy up until the advent of Goldblatt[3] Prior to that time one would define essential hypertension as a disease in which there is a more or less persistent elevation of the blood pressure in an individual in whom detailed studies, both clinically and pathologically, reveal no reasonable fundamental cause for the elevated blood pressure This description of course refers to the early stages of the disease before the development of easily discernible objective abnormalities These abnormalities were considered secondary to the blood pressure elevation With the demonstration by Goldblatt that a functional change in the circulation of the kidneys of animals produces arterial hypertension and yet renal function remains completely intact by clinical tests the definition of human essential hypertension began to change The description of the disease now had to take into account that the kidneys of animals could be the primary cause of an arterial hypertension and yet show no functional changes or pathological abnormality Following the ten years in which the Goldblatt experimental hypertension and the subsequent Page[4] hypertension of animals have been widely studied the pendulum has now begun to swing back to the original definition by Clifford Allbutt[5] Clinicians now believe that the evidence for a primary renal disorder in human essential hypertension is definitely lacking I therefore, feel that the present definition of essential hypertension is an inherited disease, in which the only demonstrable

Of 70 brothers and sisters of the parents with normal blood pressure 37 3 per cent had elevated blood pressure readings whereas of 86 brothers and sisters of the parents with essential hypertension 65 3 per cent had elevated blood pressure readings Finally the author s study of 18 families in which parts of three generations were available revealed results strikingly similar to the above findings This incidence of elevated readings in the children of hypertensive parents was obtained by merely taking the blood pressure of such people without any rest periods before making the readings This procedure was a sort of excitement stimulus which operated in people who have an inherited tendency to hypertension

A more scientific mode of applying such an excitement stimulus is the cold pressor test of Hines and Brown[13] or the author s breath holding test[14] The application of iced water directly to the hand for a given time or holding the breath for 20 seconds results in a marked rise in blood pressure in hypertensive patients Hines[15] found a striking incidence of such abnormal cold reactions among the children of hypertensive families as compared with the children of families whose parents had normal blood pressure

The Nervous Psychosomatic Possibility

This possible etiology would appear to have good grounds It has however the great disadvantage of using for etiology the intangible psyche and vasomotor center and the still unknown pharmacological psycho-physico-chemical changes that go on in nervous tissue and in contracting smooth muscles of blood vessels Those who favor this possibility or at least feel that the psychosomatic aspect plays a big part in the disease may rightly point to the fact that emotional changes are associated with much more marked changes in the blood pressure level of patients with essential hypertension than in people with normal blood pressure The blood pressure may change even 100 mm Hg systolic and 40 mm diastolic under the influence of an emotion It is very evident that at such times the emotional upset produces somehow a constriction of the arterioles throughout the body As to exactly how such constriction is mediated is open to much discussion The simplest way would be from the cortex to the centers of emotion to the vasomotor center and then through the sympathetic nerves to the end organs in the arterioles In support of such a possibility the direct severing of the sympathetic nerves by a therapeutic sympathectomy results in some cases of severe hypertension in the dramatic prolonged drop of blood pressure to normal or near normal As a further result the blood pressure of such sympathectomized patients responds little or much less than before operation to emotional and painful stimulis Further evidence for the psychosomatic relationship to the etiology of essential hypertension is suggested by the effect of sedatives, emotional and

Etiology

The best evidence at this time supports the author's belief that the etiology of essential hypertension is completely unknown However, there are many theories and experimental observations in men and animals which suggest causes of this common disorder

Heredity

Heredity plays a definite tremendous part in the production of arterial essential hypertension The author feels that it is the most important known factor in the development of essential hypertension

A definite relationship between heredity and essential hypertension and its complications was noted by Dieulafoi as long ago as 1776 and later by Raymond Broadbent, Gowers Allbutt and others[10] More recently systematic studies of family histories have demonstrated this relationship more emphatically O Hare Walker and Vickers[10] and also Weitz[10] show that a history of cardiovascular disease is frequent among the relatives of hypertensive patients Weitz showed in addition that there was an abnormally high incidence of elevated blood pressure readings among the brothers and sisters of his hypertensive patients as compared with the frequency of elevated readings in the brothers and sisters of people with normal blood pressure DeNador Nikititch[10] reported a family in which he found hypertension in the one parent studied and in 5 of 8 children Rosenbloom[10] found hypertension in 8 of 10 children in a family in which both parents died of cerebral hemorrhage The author has studied a family in which the blood pressure of every member for three generations was determined and this totalled 3[illegible] members above the age of 13[11] It was found that 100 per cent of the first generation 80 per cent of the second generation and 25 per cent of the third generation had elevated readings on two or more visits

The author then made a study of the blood pressure of 1 524 members of 277 families[1] In 780 members aged from 14 to 39 years and who represented the second generation of the families studied elevated systolic and diastolic blood pressure readings (140 mm Hg systolic and 80 mm Hg diastolic, or higher) occurred in 148 subjects The families studied were then grouped according to the presence or absence of essential hypertension in one or both parents In the families, whose parents had absolutely normal blood pressures the incidence of elevated blood pressure in the second generation was 3 1 per cent in the families in which one parent had essential hypertension the incidence of elevated readings in the children rose to 28 3 per cent in the families in which both parents had essential hypertension the incidence of elevated readings in the children reached the striking level of 45 5 per cent

many others had produced temporary hypertension by maneuvers also directed to the kidneys or ureters Among the many studies preceding Goldblatt s work should be mentioned those in which resection of large portions of both kidneys or ligation of branches of the renal artery resulted in moderate elevations of the blood pressure Goldblatt however first produced permanent hypertension in animals and was able to maintain this hypertension indefinitely Goldblatt s method is the constriction of the main artery of one kidney of dogs monkeys rabbits rats goats or sheep He used a special adjustable silver clamp over the main renal artery However the rise in blood pressure lasted only about six weeks in most of the dogs originally studied If the silver clamp on the renal artery was released or removed or if the clamped kidney itself was removed, the blood pressure returned to normal in twenty four hours or less In order to produce a persistent maintained hypertension by the clamp method for even as long as six years he found it necessary to clamp partially the renal arteries of both kidneys or partially clamp one kidney and surgically remove the other kidney In such dogs as in human essential hypertension the renal function of excretion may be perfectly normal as determined by all our present clinical tests As time goes on there is a return of the blood pressure to normal in some of these hypertensive dogs The hypertension may then be restored by further tightening the clamp about the renal arteries As further time passes even this fails in some animals probably due to the development of accessory renal circulation The use of fish skin condom membrane about the kidneys then prevents accessory circulation and therefore arterial hypertension again develops The use of cellophane by Page[4] is *unsatisfactory because it produces marked scar formation* while the condom does not produce such tissue The malignant phase of experimental hypertension may be induced by marked constriction of the clamp so that severe impairment of renal function results In such cases the animal develops pathological findings similar to human malignant hypertension Such experimental hypertension is not prevented by hypophysectomy removal of the thyroid removal of both gonads or pancreas or total sympathectomy However bilateral adrenalectomy prevents the development of this type of arterial hypertension Unilateral occlusion of the ureter will prevent the development of hypertension by unilateral ischemia and if performed after the development of hypertension by ischemia it will cause the elevated blood pressure to return to normal

The benign experimental hypertension by the Goldblatt method is often associated with the development of left ventricular hypertrophy hypertrophy of the media of the arterioles but without the development of sclerosis of the arteries including aorta or coronary vessels

If the renal veins are occluded after the animal s hypertension has developed the blood pressure returns to normal Therefore this type of arterial hypertension is of humoral origin There is no nervous reflex from the kidney since 1)

physical rest and suggestion in the successful treatment and lowering of the blood pressure level It is also of importance to note that the disease essential hypertension commences in the majority of cases with markedly fluctuant variable levels of blood pressure, which can be demonstrated to be related in great part to the emotional state of the individual It is possible to demonstrate also by study of the personality and emotional makeup of the hypertensive patient that his personality and emotional responses are of a special type and have been present from early life, in other words, long before the existence of the hypertension It is also possible to show that his symptoms such as headaches and nervousness have existed for many years, in many cases long before the development of true elevated blood pressure levels One therefore, can make a good theoretical case for the psychosomatic etiology of essential hypertension, the perpetually recurring constriction of arterioles by sympathetic impulses, produced by emotions results in the gradual hypertrophy of arteriolar smooth muscle and the development of persistently elevated arterial hypertension The latter then remains regardless of the emotional state at any one moment but even when persistent can be affected further by emotional changes and even higher momentary levels of blood pressure produced One might even go further and say that not only may the emotional nature of the individual result in the development first of variable then of permanent hypertension but also may be the explanation for the eventual death from cerebral hemorrhage for example, by causing the persistently elevated blood pressure to be momentarily extremely higher The psychosomatic study of hypertensives has been increasing in recent years so that the above simple explanation can be supported by excellent detailed psychosomatic studies to be discussed later

Experimental Hypertension

There is no good evidence that the experimental hypertensions to be described under this heading are the cause of human essential hypertension However since they represent possibilities of etiology they merit understanding and discussion As far back as 1923 Hering[16] and his students demonstrated in rabbits and dogs that persistent hypertension may be maintained for years by cutting the depressor sensory nerves which exist around the aorta and carotid sinuses Although it was possible to demonstrate that such animals would develop hypertrophy of the heart and also changes in the kidneys and arteries it is quite clear that these pathological changes and this type of hypertension have no resemblance to human essential hypertension It has been shown that this type of hypertension can be prevented[17] or cured[18] by total sympathectomy

Experimental permanent hypertension resembling human essential hypertension was really first consistently produced by Goldblatt[3] despite the fact that

that time there have been no further details or follow up studies concerning the treatment of human hypertension by Page and in a recent discussion he has indicated that progress with renal extracts has not been great The significance of the application of such renal extracts in humans as an explanation for the humoral etiology of essential hypertension has lost a great deal of its potency by the simple demonstration of Chasis[2] that nonspecific pyrogens may be the explanation for the drop in human blood pressure caused by renal extracts Chasis demonstrated that the use of such renal extracts results in the development of fever and that if instead one merely produces chronic fever in hypertensives the elevated blood pressure will often drop also One must therefore conclude that there is no scientific basis at this time for the explanation of human essential hypertension on the basis of Goldblatt animal hypertension

One should note that since Goldblatt s demonstration other methods of producing animal hypertension have been devised Among other methods is the injection of inert kaolin into the fourth ventricle of rabbits thereby causing increased intracranial pressure and consequent chronic hypertension[3] The most recent and startling method is the production of unilateral ischemia of the adrenal gland[4] Another method is the production of chronic cerebral anemia by tying off as many arteries as possible to the brain causing thereby anoxemia and increased activity of the vasomotor center followed by chronic elevation of the blood pressure[5]

Pathological Physiology

The maintenance of blood pressure normally as well as in essential hypertension is dependent on a combination of physiological actions The heart must beat with normal vigor rhythm and rate in order to pump the blood throughout the blood vessels Each normal systolic contraction of the left ventricle expels about 60 c c of blood into the aorta and in so doing causes the aorta to stretch The energy residing in the stretched aorta then exerts itself as a further force to the blood when the stretched aorta contracts back to its normal size during diastole thereby producing the diastolic blood pressure This same force operates similarly in all the larger arteries The blood passes on then to the smaller arteries and then to the arterioles The arterioles maintain a certain normal degree of tone or contraction and it is the systolic force of the ventricle and the diastolic contraction of the aorta and large arteries that forces the blood through the normal arteriolar constriction in a fairly continuous stream The consistency or viscosity of the blood also plays a part in the maintenance of normal blood pressure

Variation of any one of the above factors cardiac output rate and rhythm aortic elasticity blood viscosity and arteriolar constriction without proper com

transplanting the kidney to the neck and 2) severe destruction of the spinal cord below the fifth cervical vertebra does not prevent the development of the hypertension

The chemical nature of this hypertension apparently consists of the production of a pressor substance in the blood called angiotonin (hypertensin[19]) this results from the chemical reaction of renin produced by such kidneys and a pseudo globulin in the blood called hypertensinogen

Goldblatt feels that he has presented strong evidence that human essential hypertension is of renal origin because he has produced hypertension in animals that so closely resembles human essential hypertension He points to the fact that numerous pathological postmortem studies of human hypertension reveal disease of the renal arterioles and arteries in the vast majority of patients This argument, however may be countered with the one that postmortem studies are the very end phases of the disease essential hypertension

Does renal disease really exist in the early stages of human essential hypertension? The biopsy studies of kidneys strongly indicate that about 50 per cent of hypertensives with well established hypertension may have little or no evidence of renal vascular pathology [0] This indicates, therefore, that the renal vascular changes develop in the later stages of the disease, arterial hypertension, and are not the precursor of the established hypertension

Goldblatt theorized that the kidneys are the cause of arterial essential hypertension, starting as a functional widespread renal arteriolar spasm He feels that the widespread constriction of the small renal arterioles is comparable to his large silver clamp constricting the main renal artery He explains the successful results of sympathectomy in hypertension not as a result of widespread vasodilatation of the splanchnic arterioles but rather as a dilatation fundamentally of the renal arterioles According to Goldblatt, therefore, the same humoral mechanism of animal hypertension exists in the human However, such has not been demonstrated in human essential hypertension It is fair to say at this time that the work of Goldblatt has shown that this type of animal hypertension closely resembles human hypertension and suggests that there may be a renal humoral mechanism causing essential hypertension However it is a completely unproven theory The psychosomatic theory utilizes the sympathetic nervous impulses instead of a humoral mechanism and such sympathetic impulses could produce the same end pathological results In other words, either a humoral or nervous mechanism can produce increased peripheral resistance

The Goldblatt animal studies and the demonstration of a pressor substance in the clamped kidneys has resulted in many attempts to discover an antipressor substance with which to treat hypertension Page reported in 1941[21] the successful use of renal antipressor extracts in the hypertensive animal and to some degree in the malignant severe hypertensive human patients However, since

system. Certainly this is what one would expect in the early stages of a functional physiological disorder. The opportunities however for examining early uncomplicated cases of essential hypertension at postmortem are not frequent; it is necessary that such people die of some other disease or from accident. The ideal opportunity has been those early hypertensives who were inducted into the Army and who were killed in active combat. There is no doubt that thousands of early hypertensives have been inducted into armies. Unfortunately this material has not been utilized. Occasional reports of postmortem studies in young hypertensives, who have died of accident in civilian life, indicate the absence of pathological change by our most critical methods.

The only other opportunity for the pathological study of early essential hypertension is the use of biopsies. Unfortunately it is only muscle and skin biopsies that are possible in otherwise healthy early hypertensives. Studies of this sort have been carried out by Kernohan, Anderson and Keith [3] and amply confirmed by other investigators. Their studies have shown that in severe benign hypertension hypertrophy of the media can be demonstrated in the arterioles of the pectoralis major muscles of such patients with decrease in the width of the arteriolar lumen and increase in the thickness of the arteriolar wall. The same studies in more severe cases of hypertension, and especially in those with severe so-called malignant hypertension, indicate that the arterioles do become damaged with sclerosis, necrosis, perivascular infiltration or hyalinization of the endothelium. They have shown that the lumen of the arterioles of hypertensives becomes progressively smaller as the disease becomes more severe. There is an associated hypertrophy of the media and eventual degeneration of the muscles of the media. It may well be argued that our present histological technique is inadequate to demonstrate very early abnormality in the blood vessels which we now label as normal in early benign hypertensives. A great advance in the early pathology of essential hypertension has been made by Castleman and Smithwick[20] who studied hundreds of renal biopsies obtained during the operation of sympathectomy in essential hypertension. This study clearly indicates that even hypertension which is severe enough to require operation shows little or no change in the renal arterioles in about 50 per cent. of the cases. This finding is in striking contrast to the almost 100 per cent. arteriolar damage found in postmortems on hypertensives dying of the disease[29]. However, there are other studies of biopsied muscles which do not agree with the above data[30]. Such differences in results probably are due to the study of different stages of the disease by different investigators. The difficulties and pitfalls in the clinical determination of the severity of this chronic disease are discussed later. It seems clear, however, that past knowledge of the early pathological changes in essential hypertension, based only on postmortems on advanced cases, will require considerable revision. This applies not only to the arterioles of skin, muscle and

pensation of the other factors will result in a change in the level of the blood pressure Thus, peripheral arteriolar vasoconstriction will result in a rise in diastolic and systolic blood pressure Peripheral arteriolar vasodilatation as in syncope will result in a drop in blood pressure Marked slowing of the heart as in complete heart block will produce greater filling of the left ventricle and a greater cardiac output per beat resulting in a systolic rise of blood pressure In contrast venous pooling with inadequate filling of the ventricles will decrease cardiac output and consequently, the blood pressure

In essential hypertension these various factors have been widely studied It has been proven that cardiac output, rate, rhythm and blood viscosity are normal It follows therefore that peripheral arteriolar vasoconstriction must be the cause of the systolic and diastolic elevation of blood pressure Studies have shown that whereas the normal arteriolar blood pressure is about 55 mm of mercury, in essential hypertension it is double this figure or more[26] The blood pressure in the capillaries however is normal

Whether the arteriolar vasoconstriction is due to increase in the sympathetic impulses or to a direct action of a circulating humoral substance or is the result of inherent arteriolar muscle changes is not known The results of several studies suggest that it is not of central vasomotor origin but resides in the arterioles themselves In one study novocaine injection of the sympathetic ganglia to the upper extremity was carried out and it was found that the residual vasoconstriction of the arterioles was greater in hypertensive patients than in people with normal blood pressure [7] Therefore it is argued that a greater degree of local peripheral vasoconstriction is present in hypertensives than in people with normal blood pressure However the novocaine injection of the ganglia is necessarily carried out somewhat blindly through the skin and well may have been not complete since it is impossible to know when complete anesthetization of the ganglia is produced There may also be accessory pathways of sympathetic fibers to the blood vessels which are not novocainized at all The prompt return of the blood pressure to normal after successful sympathectomy is in favor of a central origin for the arteriolar vasoconstriction The same may be said for the results of pressor tests The pressor reaction of the arterioles of patients with essential hypertension to the cold pressor[13] and breath holding tests[14] is further evidence of the importance of an intact sympathetic nervous system for the maintenance of the elevated blood pressure the hyperreaction to these pressor tests before operation may change after successful sympathectomy to a normal reaction

Pathology

According to present histological and pathological technique uncomplicated early cases of essential hypertension show no abnormality of the cardiovascular

The kidneys pathologically show marked arteriolar disease These changes are diffuse and bilateral However as in the case of the heart in the early stages the changes are not enough to produce destruction of renal tissue and the kidneys remain grossly normal in appearance and size Eventually however the widespread marked narrowing of the arterioles results in an inadequate blood supply to many of the glomeruli and tubules so that there is degeneration of tubules and fibrosis of glomeruli with increased interstitial connective tissue and fibrosis resulting in contraction with scarring of the kidney The latter causes finally the granular appearance of the surface of such damaged kidneys and the extreme end result is the markedly shrunken contracted kidney Such kidneys show a markedly thinned cortex However the latter extreme state is reached in only a small proportion of the cases

The microscopic appearance of the kidney in essential hypertension shows varying degrees of arteriolar hypertrophy and damage resulting in varying degrees of atrophy of the kidney parenchyma varying degrees of damaged glomeruli with hyalinization and fibrous tissue Some glomeruli are enlarged and their tubules dilated due partly to obstruction from connective tissue particularly in the advanced stages of the disease However the initial process is in the arterioles with glomerular damage secondary to this interference with the circulation and then tubular atrophy secondary to the damage of the associated glomerulus It is to be noted that the arteriolar lesion involves the interlobular arterioles and the afferent arterioles to the glomeruli while the efferent arterioles of the glomeruli are within normal limits

In the so called malignant stage of essential hypertension the disease develops a relatively acute severe phase Postmortem study of such cases shows a diffuse widespread involvement of the smaller arteries and arterioles These vessels in all tissues and organs show marked hyperplasia of the intima and marked hypertrophy of the media and internal elastic lamina The lumens of the vessels are markedly reduced in size The gross appearance of organs in malignant hypertension is not characteristic of this phase of the disease

Constitutional Type in Hypertension

Physical Build of Patients

It has been shown and clinical impression supports this strongly that bodies with a broad type of build occur much more commonly than the linear type in patients with arterial hypertension This matter of body build is obviously an hereditary one and fits in with other hereditary aspects to be discussed It is part of the constitutional makeup of the hypertensive person Draper s fundamental study of the human constitution in various diseases suggested that the thorax

kidneys but undoubtedly to all of the organs of the body involved in hypertension.

Our present conception of essential hypertension is that the disease is functional in its early stages, and at such times the heart is of normal size, the large and small arteries are normal in appearance and the kidneys are normal in size and appearance. As time goes on the heart hypertrophies due to the extra work involved in maintaining blood flow through the peripherally constricted arterioles. This hypertrophy usually is slow in progress during the course of many years. The hypertrophy is fundamentally in the left ventricle which bears the burden of the extra work. The heart wall itself becomes thickened chiefly as a result of enlargement by thickening of the individual muscle fibers. However, the increase in each individual muscle fiber and in total ventricular muscle mass is not associated with evidence of increase in the number of arterioles so that there results an actual relative decrease in the amount of coronary blood flow to these enlarged muscle fibers.[31] Therefore, there is a relative decrease in the amount of oxygen available to each muscle fiber. The muscle fiber is faced not only by increased work but also by a relative decrease in its oxygen supply. The term hypertensive heart disease is applied to such hearts that are definitely enlarged beyond the normal size. The weight of such hearts that are hypertrophied may vary from the upper normal of 300 grams to a mild hypertrophy of 400 to 500 grams and in occasional instances to hearts up to 900 to 1 000 grams. As the enlargement becomes more marked, the mitral ring becomes dilated and the left auricle begins to bear an extra burden. The left auricle becomes enlarged and eventually, especially with left ventricular failure, the right auricle and right ventricle enlarge and dilate. Histological examination of such hypertrophied hearts discloses that the arterioles of the heart undergo changes similar to the arterioles in the other organs of the body. Although there is no evidence of inflammation of cardiac muscle, there is, however, frequent finding of marked fibrosis which is secondary to the involvement of the larger coronary vessel. There is a fairly high frequency of associated coronary arteriosclerosis in such hypertrophied hearts, so that one often finds evidence of old myocardial infarction due to this coronary disease. The evidence indicates a higher incidence of coronary sclerosis and infarction in patients with hypertension than in patients with normal blood pressure.[37]

As Sir Clifford Allbutt pointed out at the turn of the century[5] it is not necessary to expect to find marked large vessel arteriosclerosis in severe hypertensives. Indeed, it is very common to find pipe stem arteries in old people who do not have hypertension. The pathological changes in hypertension are chiefly in the arterioles. Nevertheless, arteriosclerosis is common in prolonged hypertension, especially in the aorta, brain and viscera. The aorta eventually may become generally dilated and lengthened so that often it is tortuous.

special field of endeavor"[38] Another observer states that "the greatest proportion of patients with hypertension are terribly tense and pursue their vocations with tremendous seriousness and worry over trivialities In consequence they are irritable They are the antithesis of the child They do not play They have no time for play They have narrow intellectual horizons"[39] In general these clinicians believe that hypertensive patients tend to be highstrung serious and overactive

These clinical impressions have been verified by more exact studies Analysis of the records of 300 hypertensive patients showed that 4 per cent had one or more of the following symptoms in early life frequent epistaxis abnormal flowing at menstruation migraine cold sweaty and cyanotic hands flushing blushing, extreme sensitiveness a highstrung and nervous temperament etc In 100 of these hypertensive patients who were questioned especially for these symptoms rather than by studied records their presence was found in 87 per cent On the other hand in 436 patients with normal blood pressure only 73 per cent of the records show such symptoms[40]

The author has studied the personality of a group of normal and hypertensive ambulatory subjects[41] The study was made with as great an attempt as possible to put the questions to the patients indirectly and without bias For example a question would be asked as follows In general throughout your life not on any one special occasion and compared to the average person of your own age with whom you have come in contact have you been the sort of person who loses his temper quickly who flies off the handle easily over little things or has it usually required a good deal to make you lose your temper? The result of this study confirmed the often mentioned clinical impression that persons with essential hypertension tend to have certain emotional and physical reactions more frequently and intensely than comparatively healthy people of the same age group and with normal blood pressure from 2 to 17 times as commonly as do the normal controls The study showed that hypertensive patients tend to be highstrung individuals who either display quick temper or are easily excited within themselves They tend to be unusually sensitive being hurt by little things In youth and often persisting to later life they tend to blush easily to be easily embarrassed and to be unusually shy In dealing with the events of life however minute they tend to be unusually serious and worry over trivialities However a much smaller percentage of the symptomless hypertensive patients admit that they are emotionally hyperactive although this percentage is definitely greater than in the control group Physically whether symptomless or not the hypertensive individual seems to be an unusually rapid walker even when in no special hurry He tends to work at his task in office or home with much more rapidity and thoroughness than the average person Hypertensive patients often eat or talk rapidly In general they tend to be unusually active physically in

of people with hypertension is long but of medium depth and width[33] He studied further the profiles of the heads of hypertensive patients and by various anthropometric techniques reached the conclusion that the head of such people resembled that of people with gall bladder disease, namely, large facial height massive ascending and horizontal rami Fishberg[34] also stated that the hypertensive has a heavy, bony skeleton, often poor muscles due to sedentary life, a broad deep chest and a short stocky build with a short thick neck However he felt that many women with essential hypertension are of the linear asthenic type Yet many writers have arrived at an opposite conclusion, that there is no relationship between body build and hypertension Both the affirmative and dissenting views have the serious shortcomings of superficial or unscientific data In anthropometric studies exact measurements of large numbers of people are necessary

The best study thus far of blood pressure and body build was made on 3 658 persons[35] In this investigation body build was expressed as an index obtained by dividing the chest circumference by the standing height This ratio of width to height was used to distinguish the narrow linear type of persons from the broad lateral type In these 3 658 persons a positive correlation between body build and blood pressure did exist Men and women of lateral or broad build sthenic type showed a marked tendency to hypertension Broad built men had systolic hypertension 4 times as frequently as the slender linear men and had diastolic hypertension 7 times more frequently In women the broad built type had almost 11 times the expectancy of systolic hypertension developing and 8 times the expectancy of diastolic hypertension developing as had the women of linear build This relation of body build to hypertension was found in all age groups but the incidence of hypertension in people of broad lateral build increased with age

Personality of the Hypertensive Patient

For many years clinical impressions have existed that patients with essential arterial hypertension have special physical and emotional reactions to life, in other words a special type of personality These clinical impressions have been variously described Hypertension occurs rather more frequently in the highstrung nervous or irritable individual' [36] ' Almost all have been of a nervous temperament throughout life They have an ill balanced personality" whose chief tendencies are ' pressure of activity and overearnestness' They are ' serious earnest conscientious enthusiastic at work, at their infrequent play and too often at table [37] They have a "certain instability restlessness a lack of confidence and shirking of responsibility During middle life they frequently are restless or ineffectual or they may be abnormally active and intensive in their

more followed by periods of depression during which their activity is much less The hypertensive person however has a drive which is perfectly steady and not broken up by periods of depression

The etiology of the hypertensive personality remains unsettled Some believe that it may be of environmental or acquired origin the result of the imitative tendency of children', which gives a pseudo hereditary aspect to it[33] Against the environmental etiology of the hypertensive personality are the groups of young individuals studied by the author as controls who although they are the children of hypertensive patients and have lived in the environment of these hypertensive parents and of their hypertensive brothers and sisters have neither the hypertensive personality nor elevated blood pressure like their brothers and sisters Others believe the hypertensive personality is primarily the result of physical influences like the personality changes in myxedema hyperthyroidism or eunuchoidism[34] It is highly possible that the hypertensive personality is of physical perhaps endocrine origin Certain it must be in the light of the author s study that the hypertensive personality present as it is in early life can be neither the result of any unusually high blood pressure nor the result of secondary vascular disease This is also borne out by the striking fact that successful treatment of patients with essential hypertension by sympathectomy does not result in any change in personality despite the drop of the blood pressure to normal levels It is also unlikely that it is due to environmental imitation of parents

Following the author s investigation of the hypertensive personality in 1932 an increasing interest in the subject seems to have been manifested by investigators who specialize in the subject of personality and psychosomatics The book on psychosomatic medicine by Weiss and English[4] devotes a chapter to the subject of hypertension with a *very excellent* description of their personality analyses of hypertensive patients

Symptoms

The modern concept of arterial essential hypertension is that the elevation of blood pressure is the first finding and the arteriolar damage is the sequence and apparently successive pathological development Similarly the symptoms of hypertension are being gradually sifted into groups with respect to their relationship to the stage of the disease For some years students of the disease have divided the symptoms into early and late groups the early group being associated with the stage of pure arterial hypertension and the late group developing as a result of the vascular changes The early symptoms occur in patients in whom after clinical laboratory and even postmortem study no adequate pathological evidence is revealed to explain these symptoms or the associated elevation of blood pressure

their domestic, occupational and social activities It cannot be emphasized too strongly that the author does not believe that every person with a hypertensive type of personality has or will develop 'arteriolar' essential hypertension It should be considered however, that many people with the hypertensive personality but with normal blood pressure may possibly have hyperreactor pressor reactions to the pressor tests and may some day develop essential hypertension Neither is it meant that every hypertensive patient has the type of personality above presented It is clear, however, that most hypertensive patients in the groups studied are of the personality type described

Not only does the middle aged hypertensive patient tend to be of a certain personality type but as far back as he can remember he has always been of that type It seems likely therefore that the hypertensive personality is present and recognizable in early life This likelihood is further confirmed by the study of a young hypertensive group whose average age was 26 and whose blood pressure was of the mild fluctuant type This group showed exactly the same type of personality reactions to life as the older group The probability that most of the persons in the younger group with abnormally high blood pressure readings of the fluctuant type are early cases of essential hypertension is enhanced also by the significant fact that about 80 per cent of them were the children of known hypertensive patients

The hypertensive personality as studied in this simple manner must be distinguished from the personality reactions of people who have an anxiety neurosis with normal blood pressure and from the manic depressive type of individuals It is well known for example that non hypertensive persons who undergo marked emotional strain, will develop hyperactive emotional responses Such emotional strain may cause not only hyperactive responses but also bodily symptoms in other words the picture of psychoneurosis However the difference between the hyperactive emotional responses of the hypertensive patients and of the psychoneurotic patients with normal blood pressure is usually one of duration, the personality type of the hypertensive person being life long whereas in most psychoneurotic patients it is only as long as the existence of the emotional upset The hypertensive personality is quite different from that of the neurasthenic individual The latter as a rule may be emotionally hyperactive for a period but is not physically hyperactive He fatigues easily, one of the outstanding characteristics of the neurasthenic He may want to do a great deal but is unable to do so physically which is in direct contradistinction to the hypertensive type

The hypertensive personality must be distinguished also from the manic depressive type which may exist without the development of a true psychosis Such people have a great deal of physical energy and enthusiasm but usually it is not a constant thing Akin to the actual manic depressive psychoses they have periods in which they are unusually energetic often lasting for months or

toms of essential hypertension commonly are mistaken for manifestations of functional nervous disorders or that the general symptoms often lead to a diagnosis of neurasthenia Allbutt said[3] ' To distinguish in a particular case between hyperpiesia (essential hypertension) in its earliest stages and neurasthenia may be a matter of some difficulty The belief that these early symptoms of essential hypertension were of psychoneurotic origin was suggested originally by Dr Jospeh H Pratt This belief was furthered and encouraged by an earlier study, in which the author definitely relieved the symptoms of 82 per cent of 40 hypertensive patients by means of suggestion[43] Therefore Dr Pratt and the author carried out a study in 1931[44] and found that there are three general characteristics of the early so-called hypertensive symptoms 1) the symptoms usually are multiple and widespread and referred to almost every part of the body 2) there is a high frequency of certain symptoms such as headache, general nervousness dizziness and fatigue 3) the duration of the symptoms or present illness is unusually long, extending for 10 15 or even 35 years in the older group studied It is found further that psychoneurotic patients without hypertension and of the same age group as the hypertensive patients show the same frequency multiplicity and widespread distribution of symptoms as in the hypertensive patients It seems however that headache and dizziness occur with slightly more frequency among the hypertensive persons than among the psychoneurotic ones with normal blood pressure All other symptoms occur in about the same frequency

In addition to demonstrating that the symptoms of psychoneurotics without hypertension and hypertensive patients are similar we analyzed the emotional lives of the hypertensive patients and attempted to correlate these with the development of their early symptoms This etiological aspect of psychoneurotic symptoms of patients is dependent on the modern interpretation that the psychoneuroses are psychogenic disorders that arise from faulty adaptation to the difficulties of life There is a resultant emotional perturbation which expresses itself physically by symptoms The development of symptoms depends on the intensity and duration of the difficulties and on the individual susceptibility Whereas a simple rebuke may cause brooding and headache in a highly sensitive and susceptible person it requires great life and-death conflicts such as those in the front line trenches to produce shell shock psychoneurosis and battle fatigue in others As a result a functional disorder of any organ or region of the body develops The diagnosis of psychoneurotic symptoms rests on three facts first the presence of symptoms which often are multiple widespread and usually not conforming in their entirety to any other clinical picture with these usually are associated symptoms and signs of emotional instability such as irritability inability to concentrate excitability and attacks of weeping secondly negative results of a physical examination and finally elicitation from the patient of the

Actually there are probably three groups of symptoms The earliest group of symptoms may begin even before the development of significant elevation of the blood pressure, may persist throughout life and later be associated with and overlap the other group of symptoms This early group of symptoms is due to the psychoneurosis which so often is associated with hypertension

To really understand the various groups of symptoms present in the disease, arterial essential hypertension, it is best to review again the development of the disease itself It is helpful to picture the disease as an hereditary one which manifests itself first in very early life as an inherited specific type of personality[41] This personality, already described, consists of hyperactive physical or emotional responses to life Next there develops a gradual elevation of the blood pressure which usually is variable and fluctuant from normal to moderately elevated levels of tension and this state may last for months, more often, years During this stage there is no pathological abnormality that can be demonstrated in the body Physiologically, however, in this stage there develops constriction and spasm of blood vessels which is entirely functional and which disappears with rest and relaxation Finally there is a stage, in which the arterioles throughout the body become organically and demonstrably damaged, and various viscera become similarly damaged This is a stage of organic disorder due to the originally long standing and recurring changes in the blood vessels This picture does not indicate what is the actual fundamental cause of the original vascular functional constriction With this review as a working background, it is easier to understand the varying groups of symptoms

Premonitory Signs and Symptoms

In the earliest stages of the disease there are a group of so called premonitory signs and symptoms that have been described by many investigators[40] The complaints of flushing blushing cold, sweating and cyanotic hands abnormal flowing at menstruation migraine fainting and dizzy spells have been described as existing long before the development of persistent hypertension and even before any evidence of hypertension has developed Most of these so-called symptoms obviously are due to varying vasomotor changes in different parts of the body

Psychoneurotic Symptoms

In addition to these symptoms and beginning at any time in early life up to and through the development of the actual elevation and variability of blood pressure there is a group of symptoms which is psychoneurotic in etiology For many years it has been recognized in textbooks of medicine that the early symp-

agement was used over periods of 1 week to 4 months with the resultant relief of symptoms in 82 per cent of 40 patients It is only in this way that one can interpret the hundreds of successes in the therapy of essential hypertension during the last three decades What it is that makes these hypertensives susceptible psychically to the difficulties of life is not clear The fundamental mechanism may be constitutional influences endocrine disturbances or other humoral factors all contributing to lessening the hypertensive patients' psychic and physical capacity for withstanding the stress of life

Vasospastic Symptoms

There are a group of symptoms which do not seem to be clearly or regularly related to a psychic etiology but which seem to be more clearly related to a vasospasm of the arterioles associated with rising or markedly high blood pressure levels Such symptoms usually are severe and more prolonged than the psychoneurotic group They consist chiefly of headaches or dizziness and marked tenseness and nervousness There are also intense spells of flushing and pallor In the most severe forms such spasm is associated with the clinical picture of what is called hypertensive encephalopathy in which the spasm of the arterioles is chiefly in the brain and in which the spasm may result not only in intense headache but also in loss of consciousness convulsions and momentary paralysis of an extremity The symptoms of the malignant phase of essential hypertension are also best placed in this group

Headaches are the most outstanding symptom of this etiological group They may be located in any part of the head but more often in the back of the head and neck They often wake the patient during the night and last for hours during the day They may last for days at a time Since the probable etiology of the symptoms is vasospasm of the arterioles and since the arterioles throughout the body are involved in the disease essential hypertension symptoms of this nature may be referred also to any part of the body It indeed also seems likely that the arterioles of the myocardium may be involved in this acute vasoconstriction and explain those patients who have prolonged attacks of angina pectoris or symptoms closely resembling this syndrome This possibility is supported by the patients whom the author has seen with such attacks of angina pectoris which have been relieved completely by successful sympathectomy for the hypertension

The etiology of this group of vasospastic symptoms conceivably may be initiated also by some marked emotional disturbance and in some cases actually seems to be so initiated However once started they seem to persist off and on for days or weeks without further clear relationship to the precipitating mechanism They no longer respond to psychotherapy and usually not well to the simple

fact that a period of important emotional stress preceded the development of symptoms The diagnosis of psychoneurotic symptoms may be corroborated further by clinical observation and psychotherapeutic success

With this working explanation of psychoneurosis it is possible to explain the early psychoneurotic symptoms of the hypertensive patient on the basis of his emotional disturbance Studies of such patients with the early symptoms will indicate that they are experiencing emotional disturbances, and that, actually their emotional burdens extend back into youth and childhood This is in keeping with the personality studies of such patients, which shows that throughout their lives they have responded with a marked emotional reaction to the more common incidents of life However, in many cases the hypertensive patient has to face really difficult situations and there seems to be an abnormally high percentage of hypertensive patients who claim they have had unhappy lives

When it comes to the new development of symptoms it is possible to discover that these symptoms really followed recent flare ups of their problems or some new emotional problem A brief example of the development of such symptoms is illustrated by the following case A patient came to me complaining of head ache weakness and insomnia of 5 weeks duration Previously she had been free of symptoms for many months During these 5 weeks the symptoms had increased in severity The patient had been known to have a blood pressure around 200/120 The emotional history indicated that one week before the development of symptoms her only son suddenly enlisted in the Air Corps, and she had been horribly upset about this since then

This simple sort of cause and effect symptom development is extremely common in the hypertensive patients It will often be found that these symptoms are unrelated to the level of blood pressure In other patients a life of problems without much interruption results in more or less continuous recurrences and presence of various symptoms It is not meant that every hypertensive patient has had great emotional difficulties and an unhappy life In many cases no such information can be elicited by such discussions A life continuously full of small annoyances however, may be disturbing to such emotional individuals They are frequently the ones with a strong family history of vascular disease Of course there is a large number of patients with early mild hypertension who have no symptoms at all

Further evidence that these early symptoms are due not to organic changes but to the emotional mal adaptation of the patient resides in the result of treatment Like symptoms of psychoneurosis they clearly respond to 1) the removal of environmental difficulties or adjustment to them 2) sedatives 3) suggestion The use of suggestion as previously mentioned was carried out by the author in the form of dilute hydrochloric acid in a red colored solution[43] This impressively tasting medicine undoubtedly non specific given with continual encour

It is important to distinguish, however the sighing type of breathing associated with psychoneurosis from true shortness of breath and the nocturia due to insomnia from true renal function impairment Similarly it is important to recognize the symptom angina pectoris as distinguished from the precordial sensitivity and discomfort complained of by patients with psychoneurosis and hypertension the hypersensitivity being of days and months duration and situated most often at the apex whereas the usual attack of angina pectoris is acute, brief and mid sternal

Damage of renal function which does not occur to any great extent in more than 10 to 20 per cent of patients is manifested first by nocturia of varying severity Nocturia at first may be in the form of waking only once a night or only a few nights a week but gradually increases in frequency The symptoms of renal function damage when progressive will present the usual clinical picture of failure of renal function

Evolution of Essential Hypertension from Earliest Stages

The earliest objective finding for the diagnosis of essential hypertension is the elevation of the blood pressure above the accepted normal level Contrary to all past definitions of this disease it is now quite clear that the disease does not suddenly evolve from a state of normal blood pressure to a persistently abnormal elevated level of blood pressure Ordinarily it consists first of mild to marked variations from normal to abnormal levels It is necessary therefore to know the level and variations of the blood pressure in the normal person

Standards of Normal Blood Pressure

The accepted standards of average normal blood pressure have been changing Formerly one considered that the age plus 100 rule was satisfactory for the systolic blood pressure but this has been shown to give much too high a normal standard As a result of life insurance data of 150 000 blood pressure determinations it was found that the average systolic ranged only from 120 mm Hg at the age of 20 to 135 mm at the age of 60[45] In another study[46] involving over 100 000 men the average blood pressure varied from 123/79 at the age of 19 to 135/86 at the age of 60 Even these standards probably are too high since many of the hundred of thousands of determinations for life insurance inevitably must be slightly elevated readings due to nervousness but would not be rechecked because they are within the acceptable insurance interpretation of normal It is therefore likely that the average normal standards are even lower It is important to note the study of the blood pressure of 6 000 prisoners[47] in whom it was found that there was no rise in blood pressure as age advanced and that the

sedatives However, this group does respond markedly to thiocyanate therapy and may be completely abolished by successful sympathectomy The vasoconstrictive nature of the hypertensive cerebral symptoms of encephalopathy is further proven by the absence of pathological findings in the brain on postmortem examination adequate to explain the recurring paralyses during life

Patients with essential hypertension, who have these severe headaches, often may give a history of similar headaches since early life long before the development of the clinical marked hypertension Frequently the headaches closely resemble the headaches of migraine with hemicrania and nausea It is of interest to recognize the close relationship between the migraine headaches of hypertensives and the migraine headaches of younger people without hypertension I have noticed that the relief of migraine headaches in younger people, in whom there is a family history of hypertension and who are of the hypertensive personality type may be accomplished often by the use of thiocyanates as successfully as in the older group with established hypertension

Organic Symptoms

This final group of symptoms is of organic etiology, due to permanent damage of the arterioles and viscera The particular symptom is related to the particular organ involved Physical damage of arterioles and arteries throughout the body may result in rupture so that epistaxis, cerebral hemorrhage, hemoptysis, hematemesis melena and hematuria may result The cardiac enlargement and failure produce shortness of breath and all the later signs of left ventricular failure Damage of renal function results in nocturia Coronary artery sclerosis results in angina pectoris

The symptom *shortness of breath* is primarily due to left ventricular enlargement, in turn due to work hypertrophy of the heart in its efforts to pump the blood through the generally constricted arterioles This shortness of breath may last for many years and advances at a very slowly progressive rate During this period shortness of breath may be present only on stairs or on great effort Part of this shortness of breath often is due to the common obesity found in the average hypertensive individual Patients become markedly accustomed to this shortness of breath so that frequently there is comparatively little complaint of it unless specifically questioned for by the doctor However the history invariably will indicate the existence of previous shortness of breath for a considerable number of months or years This symptom is neglected so often by the patient that the first thing he seems to complain of is an intense attack of nocturnal dyspnea, cardiac asthma or pulmonary edema From then on one is faced with all the symptoms associated with cardiac failure, whether due to hypertension or any other cause

tensive family and probably has a hypertensive future Of course if patients repeatedly have blood pressures above the accepted standards of normal even with very little pressor responses in blood pressure then they are distinctly ab normal subjects In other words an individual may start the pressor tests with his blood pressure at 130/88 and rise for example 15 mm systolic and di astolic Although the 15 mm is less than the average hypertensive pressure re action to such tests nevertheless the subject s rise is to a level of hypertensive nature and, therefore abnormal Such pressor tests, however, assume that suc cessful attempt has been made to obtain absolutely basal levels before applying the stimulus Under no circumstances however is it correct to expect that a person with normal blood pressure and without a tendency to hypertension should have a rise in blood pressure frequently above the accepted upper limits of normal readings in other words not above 145/90

There is no doubt that adequate excitement may elevate the normal blood pressure level to abnormal levels However all available and increasing data indicate that such temporary and repeated elevations in blood pressure indicate strongly the likelihood of future hypertension When such momentary elevations recur on numerous examinations then this possibility becomes more likely It should be noted however, that these momentary elevations in blood pressure occurring in youth and early life on excitement may often be obtained only if the examiner determines the blood pressure immediately upon the arrival of the subject and before the subject rests in a chair or on an examining table If the subject is allowed to recline and rest before determining the blood pressure these elevations may be missed

It should be recognized that there is no positive proof as yet that all people who have a hyper reactor pressor reaction to the cold test or breath holding test or to simple excitement will eventually develop essential hypertension It will require many years more of follow up of young people with positive pressor re actions or mild brief variations clinically before this can be answered It should be noted also that there are some who feel that the pressor reaction is not an indication of future hypertension[19] However there exists a good deal of evi dence to indicate that hyper reaction of the blood pressure in early life does foretell the development of hypertension in the future in the majority of subjects Some of this evidence will now be discussed

Among the data published in recent years indicating the significance of mo mentary elevation in blood pressure may be cited the following The author studied the blood pressure of 1,525 members of hypertensive and normal fam ilies[1] The blood pressure readings were taken when these people came to visit their families on the hospital wards Without more than a few minutes of ex planation the visiting subjects were asked to sit down and the blood pressures were taken at once It was found that there was a tremendous incidence 45 per

most common or modal systolic blood pressure in the ages between 15 and 60 was 115 mm Hg The modal diastolic blood pressure was 68 mm in the younger men and 73 mm in the older men They also found as high an incidence of hypertension at the age of 15 as at the age of 40 A recent study of the blood pressure of 11 000 persons[48] concluded that the normal range of systolic blood pressure for men and women at any age is from 90 to 120 mm Hg for the systolic reading and 60 to 80 mm Hg for the diastolic The study also found that a normal person reaches his mature blood pressure at about adolescence and keeps that range throughout life It concluded that normal blood pressure does not rise with age and that hypotension is an ideal blood pressure level even when the systolic dips to 80 mm Hg and the diastolic to 50 mm However until more extensive evidence like that of the 6,000 prisoners or the last mentioned study is forthcoming it is necessary to use as standards for Americans an average of 123 79 at the age of 19 and a top normal of 135/86 at age 60 and allow at the most a variation of 10 mm above these averages, so that for example a systolic reading of 145 mm Hg and a diastolic of 95 mm should be clearly considered the start of abnormality at any age Beyond this level insurance statistics show without doubt that there is a mortality increase which is in direct proportion to the blood pressure elevation

It is however, impossible to set one absolute figure as a dividing line between normalcy and abnormalcy in any given individual Moreover blood pressure never is a fixed figure so that when the blood pressure is taken from time to time in any given individual whether normal or hypertensive one will find a distinct variation in the readings The decision in an early or borderline case, therefore as to whether there is the possibility of an early case of essential hypertension will always depend on many determinations of the blood pressure at different times and on different days It is also necessary to know to what extent the blood pressure of the normal person without any inherited tendency to hypertension may vary under the circumstances of examination To know this one must utilize various data A very valuable form of data has been presented recently in the nature of the acute blood pressure elevations produced by various pressor stimuli such as the cold pressor[13] and breath holding tests[14] By this means one applies a standardized specific disturbing painful stimulus to an individual and notes the rise in blood pressure By applying such tests to individuals from hypertensive families and to individuals from normal families it is noted that there is a great difference in the degree of the rise of blood pressure to these stimuli In the normal group of patients we have corroborated the findings of Hines and Brown that the average increase of blood pressure was only 10½ mm Hg systolic and 9 0 mm diastolic According to this test also any individual whose systolic and diastolic blood pressure rises on repeated tests more than 22 mm is a so-called hyper reactor, is probably a member of a hyper

for example Failure to find variation indicates an inadequate number of observations There is however no doubt that in the severe form of the disease the variations often are limited to much narrower ranges of let us say 30 to 40 mm Hg in systolic and 10 to o mm in diastolic Nevertheless it is mo t important again to reemphasize that the blood pressure of essential hypertension has extreme variability

This variability may be demonstrated if one observes the same patients frequently enough and under conditions of relaxation as well as tension *Such lability of the blood pressure is demonstrated* most easily by taking repeated blood pressure readings during any one visit of the patient The author for example has made it a habit to have the patient sit or recline in a quiet room for a period of 20 minutes During this period the patient's blood pressure is taken every 5 minutes *and the patients are requested to relax* During this period there is no conversation and they are left alone in the room between readings of the blood pressure The initial blood pressure is taken immediately after the patient has sat or lain down (Chart 1)

Such observations show that from minute to minute the hypertensive patient has widely vary ing blood pressures depending markedly on his physical and psychical stimuli The blood pressure usually is lower in the morning than in the evening On a warm humid day the blood pressure level is *lower than on a cold day* *Daily or weekly records by such means of rest during the* course of months or a year show widely fluctu ating levels in untreated patients Such lability will occur in cases of hypertension of long dura tion many with heart disease retinal changes or renal damage As a matter of fact it will be found that on some days after the patient has been rest ing in a comfortable chair in a quiet room the blood pressure will drop to a normal level momentarily Even more striking is the fact that occasionally it is seen to be normal without rest

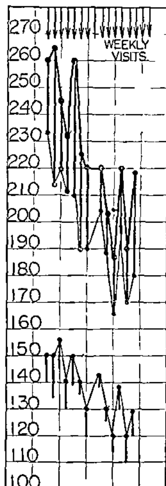


CHART 1 Blood pressure vari ations at weekly visits over a 4 month *period without treatment* The upper black dots are the in itial readings at the start of a 20-minute rest period The ver tical black column beneath the dots represents the range during the rest period

cent of elevated and abnormal blood pressure readings among the children of hypertensive parents and an extremely slight incidence, 3 5 per cent, of elevated readings among the children of families in which both parents had normal blood pressure This suggested strongly that the momentary elevation in blood pressure of the children of the hypertensive families was not merely due to the emotional excitement of the examination but to the effect of this emotional excitement upon an hereditary tendency to over react of the subjects vasomotor systems and/or arterioles

Hines[50] also has furnished important data by showing that of hundreds of people who visited the Mayo Clinic many years ago, and who upon their entrance had blood pressure readings around 140/90, the follow up of such patients showed an extremely high incidence of hypertension as compared with patients who entered the Clinic with absolutely normal initial blood pressure readings

In a 5 to 10 year follow up study of the systolic blood pressure of 155 young students Diehl and Hesdorffer[51] also found much more frequent hypertension in those whose blood pressure at the earlier ages showed elevations of blood pressure than in those whose blood pressure at the earlier ages was consistently within normal limits

Reports of the follow up study of large numbers of regular officers of the United States Army who were examined on Army entrance years ago show similar data namely that momentary emotional elevation of blood pressure at the initial Army examination strongly indicates that future hypertension is to be expected[5] This is quite in keeping with the author s long held opinion that emotional hypertension does not exist without an underlying hypertensive tendency in most of the cases

The evaluation of a mildly or moderately elevated blood pressure reading in a young person requires the ruling out of any immediately preceding exercise which in, and of istelf may elevate the blood pressure systolic especially in normal persons without hypertensive tendencies The presence of a markedly elevated pulse rate in such cases is more suggestive of a non hypertensive tendency but does not prove the point It should also be emphasized that some of these previously mentioned studies as well as my own clinical experience indicate that in these early subjects of essential hypertension systolic elevations in blood pressure may be the sole finding and only a small percentage may have accompanying diastolic elevation

Details of the Variability of the Blood Pressure in Hypertension

Variability is the outstanding characteristic of the blood pressure itself and the disease itself There is practically never any case in which there is an absolutely fixed constant level of blood pressure within a small range of 10 mm,

tionship between the frequency of the visits of the patients to the doctor and the height of the blood pressure that is to say the more frequent the visits the lower the blood pressure within limits[55]

This is seen for example in Chart 2 It is seen that when a patient was followed for six months at monthly intervals the systolic blood pressure varied between 254 mm and 232 mm Hg and the diastolic blood pressure between 130

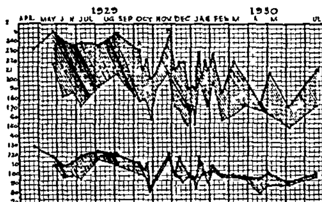


CHART 2 Blood pressure readings of M B aged 62 showing marked retinal arteriolarsclerosis, slight cardiac enlargement by orthodiagram and normal renal function known hypertension for 4 years The 2 curves that bound the upper hatched lines represent the systolic blood pressure variations not only from visit to visit but also at each visit The variations at each visit (due to from 10- to 20-minute sitting rest periods) are represented by the vertical distance between the 2 symmetrical points The 2 curves bounding the lower hatched lines represent the same features in the diastolic blood pressure

and 114 mm On the other hand when followed at weekly intervals for the next 6 months the systolic blood pressure varied from 232 to 174 mm Hg and the diastolic blood pressure from 1 4 to 80 mm

This sort of phenomenon can be demonstrated almost always The probable manner in which the frequency of visits operates on the blood pressure is by means of the comparative nonchalance and relaxation which comes on frequent repetition of visits as compared with the relative excitement of infrequent observations Hypertensive patients who come in to the office comparatively infrequently express great pleasure and excitement in seeing the physician and this pleasure is distinctly reflected by an elevation of the blood pressure level Visiting at weekly or more frequent intervals results in the absence of this exuberant Glad to see you how have you been reaction and gives a definitely lower blood pressure reading

ing, justifying the paradoxic statement that the disease essential hypertension may exist with a normal blood pressure The author followed 76 patients with essential hypertension over periods ranging from two months but chiefly over periods of a year or more and found that 43 patients or 56 per cent showed a normal blood pressure at least once during this period of many observations[53] On the whole such patients, who have an occasional or frequent drop to normal tend to be of slightly younger age than those, who have a blood pressure persistently above the normal levels When the author studied this group their average age was 52 years as compared with 62 years for patients who did not drop to normal However, in this group with these occasional drops to normal there were only rare cases of renal function impairment, although several had had cerebral hemorrhages

Another aspect of the variability of blood pressure in essential hypertension is the variability of the diastolic blood pressure Many textbook statements emphasize that the diastolic blood pressure has only slight variability, particularly in comparison with the systolic blood pressure This however, is not the fact Observations of patients in a manner similar to the above described 20 minute rest periods has shown the author that the diastolic blood pressure fluctuates widely in hypertensive patients, even in patients with severe vascular damage[54] Such fluctuations are particularly evident from visit to visit and without treatment

The degree of fluctuation depends to some extent on the number of observations made on the patient the more frequent the observation the greater the fluctuation noted The author's experience indicates that the diastolic blood pressure fluctuates by proportion as much as the systolic blood pressure The diastolic blood pressure has been found to vary as much as 66 mm In a group of 24 patients with systolic readings usually 200 mm Hg or more the total diastolic variation during rest periods and during many visits was an average of 43 mm In a group of 22 patients whose systolic variations were usually between 160 and 200 mm Hg the total diastolic variation of all diastolic readings during total observation and rest periods averaged 37 5 mm

In 30 patients with systolic blood pressure of 160 mm Hg or less the diastolic variations averaged 30 mm By actual percentage variation it was found that the fluctuation of diastolic was as great as that of the systolic blood pressure It is of great interest to note also that as much as 66 mm Hg variation was found in the diastolic blood pressure of one patient at one visit The variability of systolic and diastolic blood pressure at any one visit is partly proportional to the amount of time that the patient rests at the visit

The lability of the blood pressure in essential hypertension results in the production of another syndrome which should be thoroughly known by all students of the subject of hypertension There seems to be in most cases a definite rela

rest and the later readings after rest in the clinic approach closer to the initial home readings The initial home readings being taken with the patient already relaxed cannot drop very much further on rest and therefore home and clinic readings taken after rest periods are closer to each other Further comparison of home readings after the patients had rested in a chair for 10 minutes or so with the clinic readings after the patients had rested in the clinic for a similar period show that the differences although present were not as great as the differences between the initial readings

It was found that the difference between home and clinic readings was in general the same in those patients who took their own readings and those who had some member of the household take the blood pressure However in several instances a change from having a member of the household take it to having the patient himself take it resulted in somewhat different levels of blood pressure being found The effect of different individuals on a patient is related to the personality of the individuals who take the blood pressure In one case when a calmer more relaxed daughter took over the duties of taking readings the readings were lower This effect of the doctor or nurse on the patient is seen often in practice where an excitable brusque doctor will obtain much higher readings than the calm physician

Observation of the home blood pressure readings has shown both the patients and physician the relationship of the level of blood pressure to strain worry work play etc One patient for example noted regularly that when he played cards in the evening his blood pressure was higher than usual when he arrived home despite the fact that he had not noticed himself excited during the game Others noted the relationship of a cold house to high readings Still others have noted the relationship of headaches and other symptoms to their blood pressure level We have noted also the relationship of environmental problems in the patients lives to elevation in blood pressure In no case was neurosis or harm produced by the home blood pressure method

Evolution of the Disease

Prolonged clinical observations of subjects with momentary elevation of blood pressure have been made by the author over periods of 5 10 and 15 years It is found that no general or particular pattern in the development of the elevated blood pressure can be outlined However the largest group of such patients continue to show varying levels of blood pressure at different times The tendency of the maximum levels to increase is usually a very slow one over the course of years The variations in any one individual however seem to maintain a specific pattern For example a patient who during the initial period of observation years before showed a momentary rise chiefly in the systolic readings

Home Blood Pressure Readings

The present knowledge of the blood pressure levels in essential hypertension is based entirely on measurements of blood pressure readings made by physicians largely in the clinic or office No data has been available regarding the level of blood pressure which obtains during a patient's normal daily activities away from the doctor The importance of such information for a complete knowledge of the life history of hypertension is evident

In 1930 Brown[56] reported the study of a patient with essential hypertension who took his own systolic blood pressure for three years However no diastolic readings were made, and no correlation was made between the clinic and home readings Goldshine and the author have studied many hypertensive patients in the past eight years by means of home readings and compared the latter with clinic and office blood pressure readings in the same patients In these studies the patients or some member of the household were taught to take blood pressure readings In our initial study of this aspect of blood pressure variation we studied 34 cases of essential hypertension[57] In these 34 people we analyzed 2,800 clinic readings and 40 000 home readings In every one of the 34 cases of essential hypertension the blood pressure readings taken at home by the patient or some member of the household were lower than those taken at the clinic by the doctor These differences between home and clinic readings varied markedly in each case depending on whether we analyzed the readings made during or after rest The maximum differences between home and office are found when one compares the readings made immediately before resting when the patient sits down, whether at home or in the office Since the common office method of taking blood pressure readings is to record the initial reading without rest differences between our initial clinic and initial home blood pressure readings may be applied to the experience of the general practitioner Under such conditions the home blood pressure level may be as much as 70 mm Hg systolic and 36 mm diastolic lower than the clinic or office level Such great differences do not indicate occasional differences but general ranges of blood pressure over an average period per patient of 104 weeks of special clinic study and 23 weeks of subsequent home blood pressure study Although the diastolic blood pressure did not vary as much as the systolic in 23 per cent of the cases there was 20 mm or more difference between the home and clinic diastolic readings The great difference between the initial readings at home and in the clinic appears to be due to the excitement and tension associated with the visit to the clinic or doctor's office In his home the hypertensive patient presumably is more relaxed and therefore his initial blood pressure reading under such circumstances is lower

It appears reasonable that since the patient's excitement is much more intense in the clinic than in the home, the clinic readings should drop the most on

rest and the later readings after rest in the clinic approach closer to the initial home readings The initial home readings being taken with the patient already relaxed cannot drop very much further on rest and therefore home and clinic readings taken after rest periods are closer to each other Further comparison of home readings after the patients had rested in a chair for 10 minutes or so with the clinic readings after the patients had rested in the clinic for a similar period show that the differences although present were not as great as the differences between the initial readings

It was found that the difference between home and clinic readings was in general the same in those patients who took their own readings and those who had some member of the household take the blood pressure However in several instances a change from having a member of the household take it to having the patient himself take it resulted in somewhat different levels of blood pressure being found The effect of different individuals on a patient is related to the personality of the individuals who take the blood pressure In one case when a calmer more relaxed daughter took over the duties of taking readings the readings were lower This effect of the doctor or nurse on the patient is seen often in practice where an excitable brusque doctor will obtain much higher readings than the calm physician

Observation of the home blood pressure readings has shown both the patients and physician the relationship of the level of blood pressure to strain worry work play etc One patient for example noted regularly that when he played cards in the evening his blood pressure was higher than usual when he arrived home despite the fact that he had not noticed himself excited during the game Others noted the relationship of a cold house to high readings Still others have noted the relationship of headaches and other symptoms to their blood pressure level We have noted also the relationship of environmental problems in the patients lives to elevation in blood pressure In no case was neurosis or harm produced by the home blood pressure method

Evolution of the Disease

Prolonged clinical observations of subjects with momentary elevation of blood pressure have been made by the author over periods of 5 10 and 15 years It is found that no general or particular pattern in the development of the elevated blood pressure can be outlined However the largest group of such patients continue to show varying levels of blood pressure at different times The tendency of the maximum levels to increase is usually a very slow one over the course of years The variations in any one individual however seem to maintain a specific pattern For example a patient who during the initial period of observation years before showed a momentary rise chiefly in the systolic readings

tends to maintain such a pattern of systolic elevation during the course of many years with only slight increases in the diastolic blood pressure Similarly, those young patients, in whom the diastolic elevation is of moderate degree and more pronounced than the systolic elevation for example, up to 100 mm in the early years of observation usually continue to show such elevations of diastolic as well as systolic on subsequent visits Thus they tend to continue to have a narrow pulse pressure It is noted also that those, who tend to have a tachycardia with the elevation of their blood pressure, will continue to show tachycardia on repeated observation over the course of years The author's experience suggests that tachycardia is more common in those with only slight diastolic elevations in readings than in those who tend to show more pronounced diastolic elevations in addition to systolic elevations Although the early onset of the disease as above described comes in comparatively young people, there is no reason why the same picture cannot commence first at any time after, let us say, the age of 50 The author s experience suggests that such does occur

On the whole therefore, essential hypertension so far as its existence is evidenced by blood pressure elevation is a disease for the most part of many years' duration and of comparatively benign degree (Chart 3) The benign nature of this disease is evidenced, for example, by the experience and attitude of life insurance companies who will accept those individuals whose blood pressure will drop to levels below the upper limits of normal after rest Similarly during World War II army induction centers have accepted thousands of hypertensive young men whose blood pressure dropped on rest, for example, below 150/100 Yet in the overwhelming majority of the above subjects we are dealing with the early stages of essential hypertension which becomes more marked as the years go on Since life insurance companies know from their mortality data that individuals whose blood pressures are in the upper limits of normal are satisfactory insurance risks it is evident that the vast majority of these subjects live many years during the process of the evolution of their disease Parenthetically however such individuals who at the start of an examination have elevated readings and after resting have readings within the accepted normal levels undoubtedly have a lesser longevity than people with absolutely normal blood pressure readings at the start of an examination

As already indicated the usual duration of the disease is many years with probable averages of 15 to 20 years However the disease may last in many instances for 30 years or more or may evolve rapidly during the course of a few months to a year into a most severe state The usual group however which lasts 15 to 20 years has gradually increasing systolic and diastolic levels during the course of the years, but this benign slow course may in some instances evolve at any time into a rapid more severe elevation of blood pressure with its accompanying severe syndrome of symptoms and signs These latter cases with

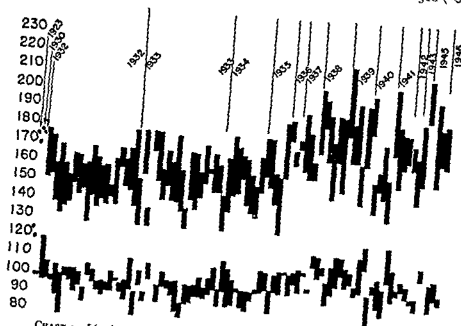


CHART 3 Blood pressure readings in a patient over a 23 year period During the past 14 years the readings have been taken at each visit over a 20 minute rest period Each vertical black column represents the blood pressure variations at an individual visit The upper columns represent systolic variations at each visit and the lower columns represent diastolic variations

rapid development of the disease are relatively uncommon and are termed severe so-called malignant hypertension

Severe Malignant Hypertension

By definition the outstanding and distinguishing finding in this group is the retinitis with varying degrees of edema of the optic discs and retinae in all cases In fact the original study of patients with so called malignant hypertension specifically reported only patients who had some degree of blurring of the optic discs[35] If one subtracts these ocular findings in a given case then the remaining clinical picture of any one examination is indistinguishable from severe benign hypertension In malignant hypertension blood pressure levels are very high so that a diastolic level of 120 or more is the rule However the same sort of blood pressure level is found in many benign patients without the retinitis It is impossible to forecast which of these benign patients will develop the typical retinitis and therefore the malignant phase of the disease Once the malignant

phase of the disease is discovered, the life expectancy is comparatively brief. In one series of 81 patients 91 per cent died within 51 months, the majority within 2 years, and the average length of life after diagnosis was 8 months[33]

Physical Findings

In the early stages of the disease, when the only manifestations are the abnormal fluctuations of the blood pressure and the objective evidences of the hypertensive personality reactions, the physical examination will disclose no other abnormality. Such a negative physical examination is clearly to be expected since the disease is more or less a functional one in the early stages. Negative findings often persist for many years and the physician is often on the defensive to explain the frequent symptoms such as headaches and nervousness of which these patients commonly complain. The usual enigmatic explanation is that "You are too nervous"

While the blood pressure fluctuation continues during months and years there is a gradual tendency of the blood pressure to be more often at an abnormal level than at a normal level. In this beginning stage of more frequent abnormal readings careful examination of the fundi of the eyes will reveal to an ophthalmologist or experienced internist that the small arteries and arterioles are slightly narrower than normal. The author has proven this point in large numbers of patients by sending both early hypertensive patients and patients with normal blood pressure to an ophthalmologist without telling him the level of the blood pressure. The findings by this ophthalmologist of slight narrowing of the arteries in the fundi was strikingly and closely correlated with the patients who had the early mild fluctuating hypertension. Although no narrowing was found in the subjects with normal blood pressure, slight abnormality was found in most of the young hypertensive patients. This narrowing of course would not be present in all the young hypertensives but is dependent on whether there is beginning spasm and changes in the arterioles. In this stage physical examination of the heart or of the radial and temporal arteries will show no abnormality. The examination of such patients will, however, usually disclose that they are very often obese or at least moderately above the average normal weight for their age and sex, and usually they are of the broad, sthenic build.

During the course of still further months and years the persistent elevation of the blood pressure will be accompanied by more definite physical signs. These signs consist of very definite, easily recognized narrowing of the arterioles in the fundi with slight to moderate nicking of the veins where the arteries cross them and irregularity in the caliber of the small arteries and arterioles so that they develop the appearance as if someone had partially tied a fine thread about the vessels at different points. The heart in an increasing number of cases then will

be found to have its apex impulse just beyond the normal mid-clavicular line and the cardiac impulse will be found to be a forceful powerful thrust Radial arteries may or may not be found to be somewhat diffusely thickened Eventually if the patient lives long enough and this may require many years the heart becomes markedly hypertrophied and is accompanied by the previously mentioned symptom of shortness of breath The second aortic sound becomes somewhat accentuated and systolic murmurs of varying intensity will be heard over the aortic regions or mitral areas In the extremely advanced stages of heart hypertrophy in this disease it is not uncommon to hear a high pitched aortic diastolic murmur of mild to moderate intensity The aortic murmur is undoubtedly on a functional basis since postmortems in such cases usually do not disclose incompetence of the aortic valve The term hypertensive heart disease is variously applied but should be used when one can demonstrate by x ray or physical examination the presence of definite cardiac enlargement due to hypertension regardless of the presence or absence of shortness of breath Eventually the left ventricular cardiac hypertrophy reaches its maximum and all the signs of left ventricular failure develop This in turn may be followed by right sided heart failure with the signs of peripheral edema and enlarged liver

Accompanying the changes in the heart one may note on physical examination a pulsation in the region of the jugular notch and also at the anterior basal portion of the right side of the neck This pulsation is presumably due to a dynamic dilatation of the aorta and innominate arteries as well as an elevation of these structures by the enlarging heart Postmortem in such cases does not disclose organic aneurysm of these vessels which were obviously dilated and enlarged only during life

Eventually the ocular fundi show more and more marked evidences of the findings already described and if the disease becomes acutely intense one finds a marked generalized spasm of the arterioles which is easily recognized With this there frequently are seen scattered fresh pin head size or flame shaped hemorrhages often along the course of the arteries or veins At later examinations areas that previously showed fresh hemorrhages will be found to change to white spots and not infrequently one may find unusual crystal like deposits in areas of previous hemorrhage

In some instances an extremely severe phase of the disease termed malignant hypertension develops and in all of these cases it is characteristic that the optic discs become blurred at first along the nasal border eventually the entire disc and finally with marked elevation of the discs The adjacent retina often may become pale cloudy and edematous This edematous elevation may be as much as 6 diopters but usually averages about 2 diopters When the edema or hemorrhages involve the macular region blurring of vision develops Although on rare occasions a mild retinitis may recede spontaneously to normal the vast majority

of such cases continue or progress during the remaining months or few years of life Rare cases with blurring of discs and vision lasting up to 4 years have been seen Such patients with retinitis may feel comparatively well and be able to carry on reasonably active lives For months their cardiac, renal and cerebral function may remain good Finally one or more of these organs will develop rapid impairment of function, and death from cerebral hemorrhage, cardiac failure or renal insufficiency ensues

X ray Studies

X ray of the Heart

Clinical examination of the heart in hypertension is for ordinary purposes quite adequate for the observation and treatment of patients with this disease As already mentioned the majority of early or mild cases do not have enlargement by clinical examination unless the disease has lasted a long time or assumes a severe stage Ordinary percussion will disclose the gross enlargement which occurs in the majority of these long standing or severe cases However the question of slight cardiac enlargement in the early stages of the disease is not best answered by percussion As a matter of fact the existence of cardiac hypertrophy in the early stages of hypertension cannot always be clearly answered even by the 7 ft heart film in any given individual case The reason for this difficulty is that we usually do not know the normal heart size of a given individual prior to the development of his hypertension The use of statistics to determine the upper limits of normal heart size for a patient s height weight, age and sex actually allow 1 to 2 centimeters of variations for an individual Comparison of heart size with chest diameter by x ray gives an even greater range of normal For these reasons, therefore a 7 ft heart film is a most desirable procedure to employ in an early hypertensive when seen during the first months of his disease It will most definitely give the physician control measurements and the normal cardiac appearance which can be compared with future x rays in order to determine whether the disease is producing any increase in heart size or change in configuration From such data which the author has obtained during the course of many years, he has found that a hypertensive heart may enlarge several centimeters during the course of years and yet still be at the border of the accepted normal Further evidence of this nature is obtained in patients who have been sympathectomized in whom the heart size preoperatively was merely at the upper border of normal Following successful sympathectomy the heart may decrease in size from the apparently normal preoperative size Decreases in heart size after sympathectomy may be partly due also to the postoperative postural hypotension with subsequent poor filling of the heart As the disease advances

the enlargement of the heart particularly of the left ventricle becomes more and more evident There is an early convex rounding of the left border and there is also an increase of mild to moderate degree in the width of the aorta Eventually the 7 ft x ray of the heart will show a generalized marked enlargement due to both left ventricular and right sided heart hypertrophy and dilatation The latter finding follows the development of clinical evidences of left ventricular weakness and failure The greatest value however of the 7 ft heart film in the hypertensive individual is in the recognition of the earliest evidences of heart hypertrophy and therefore the change from the functional to the organic stage of the disease

Many patients with essential hypertension existing for many years will have no discernible cardiac enlargement by 7 ft heart film In many such patients the clinic or office blood pressure level may be extremely high especially in the systolic blood pressure The probable explanation for the absence of work hypertrophy of the left ventricle in most such cases is that the blood pressure really does not maintain such high levels most of the time In such cases it is probable that only during the clinic or office examinations are the blood pressures at marked heights while at home and during the greater part of the individual s daily existence the blood pressures are only at mildly elevated levels Goldshine and the author in unpublished data have found this to be so in many cases Patients in such cases with hospital records of moderate to marked hypertension of 10 to 20 years duration have had normal sized hearts and in some of these the home blood pressure readings now are only slightly above normal In these cases it should be emphasized that the elevation of blood pressure usually is more marked in the systolic than in the diastolic readings This does not however imply that a marked systolic elevation of blood pressure without marked diastolic elevation does not produce cardiac hypertrophy We have observed many cases in which marked systolic elevation and only slight to moderate diastolic elevation of the blood pressure are associated with definite slight to marked cardiac hypertrophy We have noted also moderate systolic elevation without any diastolic elevation at all associated also with definite left ventricular hypertrophy without other cause On the whole however left ventricular enlargement of the heart in essential hypertension seems to be most closely related to the existence over a reasonably long period of time of both systolic and diastolic elevation of blood pressure Such hypertrophy also seems more definite and marked in cases where the diastolic elevation of blood pressure is more pronounced It is noteworthy also that there are a number of cases of hypertension in whom only a moderate elevation of systolic and diastolic blood pressure will result in marked hypertrophy of the heart whereas the same elevation in blood pressure will in the majority of hypertensives be inadequate to produce any enlargement of the heart

X ray of the Kidneys

Involvement of the kidneys produces no objective physical signs but does produce changes in the urine and tests of renal function. Flat films of the abdomen will clearly outline the kidneys and indicate their size. In essential hypertension involvement of the arterioles of the kidneys will in 15 to 20 per cent of the patients result eventually in fibrous scarring and marked decrease in the size of the kidneys. Such decrease may be extremely marked, and the resulting contracted small kidneys may be demonstrable on the x ray film.

The experimental studies of Goldblatt in the production of animal hypertension have focused the attention of clinicians upon the kidneys as a possible etiological source of hypertension. As a result it has become a somewhat routine matter to take so-called intravenous pyelograms of the kidneys. These are obtained by injecting diodrast intravenously and taking x rays of the kidneys, ureters and bladder at five minute intervals. By this means one can observe the excretion of the diodrast into the pelves of the kidneys, ureters and bladder. The rate of the excretion and its concentration in the pelves give a clear idea of the ability of the kidneys to concentrate substances. However the use of the intravenous diodrast pyelogram is not fundamentally for the purpose of disclosing the ability of the kidneys to concentrate because clinical concentration tests give this answer much more simply. Such pyelograms have been used rather routinely in the study of hypertensives for the purpose of discovering evidences of unilateral or bilateral pyelonephritis or some other unilateral primary renal disease. Such abnormal findings in essential hypertension are not the rule. The number of cases of nephrectomy with proven cure of well studied hypertension may be counted on the fingers as compared with the millions of people who have essential hypertension. For that reason the routine use of intravenous pyelograms is not "a must" in the study of the average patient with essential hypertension. The routine use of intravenous pyelograms in the preoperative study of hypertensives also does not seem justified since it is a somewhat expensive procedure for the average individual. Only after all other studies of a case indicate the desirability of a sympathectomy should the patient be studied by intravenous pyelogram.

The kidneys have been studied by x ray with the hypertensive patient both standing and lying down and it has been shown that the kidneys tend to change position markedly. From this it has been argued that the ptosis of such kidneys may result in interference with the blood supply to the kidneys with a resultant ischemia and production of hypertension[59]. Such explanation, however, does not jibe with the common existence of hypertension in young people in the recumbent position and in whom the kidney therefore would not be expected to be ptotic. Similarly studies by intravenous pyelograms stating that patients

with essential hypertension tend to have a higher percentage of intrarenal pelves also seem to have no clear relationship to the etiology of hypertension[60] Finally other x ray studies of the kidneys in hypertension have shown a comparatively high percentage of varying abnormalities of the genitourinary tract[61] but here again their relationship to the etiology of hypertension seems extremely unlikely

Electrocardiograms

As with all objective examinations in essential hypertension the early stages of the elevated blood pressure usually are associated with a perfectly normal electrocardiogram This status may last for as many years as the heart escapes hypertrophy or damage of the coronary arteries As in the case of x ray of the heart size in the early stages it is extremely wise to determine the normal appearance of the electrocardiogram as early as possible after the disease is recognized or suspected In this way beginning evidences of cardiac change usually will be noted before signs of percussion or auscultation show changes

Many hypertensives tend to be overweight and the majority of them are of the broad stocky build For that reason the physician should be acquainted with the normal electrocardiograms to be found in people of this build who do not have hypertension In this stocky broad type of chest the diaphragms tend to be elevated and as a result the heart tends to be displaced more in a transverse direction As a result of this there is often found some left axis deviation and occasionally a prominent Q wave in lead 3 Usually however accompanying the electrical axis deviation the T wave in lead 3 is inverted when the left axis deviation is due to shift in the position of the heart

Some of the earliest changes in the electrocardiogram of essential hypertension are in the electrical axis The left ventricular hypertrophy results in left ventricular preponderance in the tracing The findings in the electrocardiogram in essential hypertension are really the usual findings of left ventricular hypertrophy of increasing degree and the same electrocardiographic findings are found regardless of the cause of such ventricular hypertrophy The left axis deviation consists of a prominent S wave in lead 3 and as time goes on a prominent S wave in lead 2 The T wave in lead 3 usually is erect In the chest leads the QRS waves are chiefly in a negative direction and occasionally entirely downward This is more true in lead CF2 but does occur also in leads CF4 and CF5

As time goes on and the left ventricular hypertrophy becomes more marked there is added a depression of the S-T intervals in lead 1 and frequently in lead 2 with inversion of the T waves in leads 1 and 2 Observation of these patients by means of electrocardiograms over the course of years will show these changes to be gradual rather than an acute sudden process The S-T depression may be extremely slight at first but in the course of years it may be as much as or 3 mm

below the isoelectric baseline of the electrocardiogram The S-T interval in lead 3 is correspondingly elevated above the isoelectric line The left axis deviation becomes more marked and the T wave in lead 3 is more constantly found erect In this more advanced stage the QRS waves in the chest leads also change from the normal, positive erect QRS waves to the more frequent downward QRS waves in lead CF2 and downward QRS waves in leads CF4 and CF5 in many cases Also in lead CF4 and CF5 the S-T interval often is depressed and the T wave inverted in a manner strikingly similar to the appearance in lead 1 The S-T depressions of left ventricular strain and hypertrophy with accompanying inversion of the T wave are to be distinguished from the acute coronary S-T changes and from digitalis effect In left ventricular strain and hypertrophy the S-T interval is depressed and is bowed convexly upward, and the T wave also is below the isoelectric line In the acute coronary type of change the S-T interval is elevated above the isoelectric line, while the T wave is below the isoelectric line, although the S-T interval also is convexly bowed upward On the other hand in the digitalis S-T interval and T wave the S-T interval is below the isoelectric line and is either a somewhat straight line from the S to the T with inclination downward or is a concave bowing below the isoelectric line merging into the beginning of the T wave which also is below the isoelectric line However, such differentiation is not always clear cut or simple Increasing hypertrophy of left ventricular muscle produces changes in conduction direction and conduction time so that the QRS waves widen somewhat and resemble intraventricular block but measure less than 0 1 second

Increasing ventricular hypertrophy in essential hypertension and in general is not associated with a corresponding increase in the blood supply of the ventricular muscle[31] There is no growth of capillaries of the heart muscle and at most there can be a dilatation of them Eventually the muscle mass becomes entirely inadequately supplied by the blood flow through the unchanging supply of coronary vessels There then develops a state of relative coronary insufficiency and the electrocardiogram then assumes the usual appearances of coronary insufficiency seen also in many other conditions Eventually also the coronary circulation becomes impaired by narrowing of the larger coronary arteries, which is termed coronary sclerosis so that the narrowing of these large vessels results in marked restriction of the ordinary blood flow and even greater coronary insufficiency results The electrocardiogram then begins to show the evidences of myocardial damage with typical coronary contours of the S-T intervals and T waves There are also the abnormalities of QRS waves due to injury which results in intraventricular block bundle branch block QRS notching and slurring and ventricular ectopic rhythms

The annual examination of the patient by electrocardiograms is a real help in gauging the progress of the disease and its effect upon the heart Absence of

abnormality in the electrocardiogram of essential hypertension is helpful evidence of the benign state of the disease and of relatively unimpaired cardiac function Conversely rapid changes in the electrocardiogram of hypertensive patients even without other evidence of change in cardiac function have great significance that the disease is exacting a toll on the heart and that whatever measures of treatment are available should be more seriously considered and employed Chart 4 shows the electrocardiographic changes in a patient before and after sympathectomy

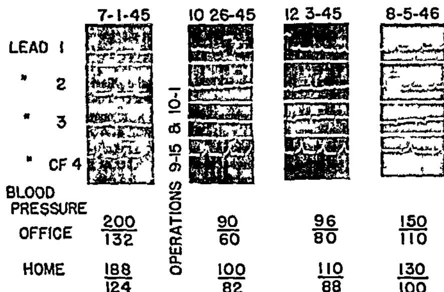


CHART 4 This shows changes in the electrocardiogram before and after lumbothorac sympathectomy Within 25 days after operation inverted T waves in leads 1 and 2 have become upright This change became progressively more marked in the course of the next 10 months All tracings taken with the patient recumbent and the standard deflection was 1 cm per millivolt

OTHER LABORATORY DATA

The most important laboratory data for the evaluation of a patient with essential hypertension concerns the status of the renal function The best tests of renal function do not disclose evidence of damage until actually a very large amount of renal tissue has been destroyed As a matter of fact removal of one kidney will not be discernible by function tests It is therefore likely that when any evidence of renal function damage is obtained by laboratory data there already is a very marked amount of destroyed renal tissue

In recent years the use of the urea clearance test, diodrast excretion test and inulin clearance test have been presented as tests of great delicacy for determining early impairment of renal function These tests, however, are comparatively complicated and so not practical for general clinical use

The most delicate test for practical clinical use is the concentration test By this test one attempts to put the kidneys at their maximum working ability to produce a concentrated urine The sole principle is to restrict the intake of fluids at the same time that the body has an adequate supply of protein in the food so that the urea and other urinary constituents may be excreted Various modifications of the original Volhard dilution concentration test have been made during the course of many years In reality it does not matter what test is used provided there is an adequate limitation of fluids for an adequate length of time and some of the pitfalls of the test in general are avoided There seems to be no significant information to be obtained by doing the dilution phase of the dilution concentration test

Fishberg has modified the concentration test in a manner which is fairly satisfactory[63] The patient has his regular evening meal at 6 P M on the night before the test This meal should contain a goodly amount of protein food and I advise patients to eat at least ½ pound of meat, fish, chicken or 3 eggs Together with this some bread butter and potatoes make an adequate meal Fishberg permits the patient to have up to 200 c c of fluid with this meal but in my experience this is undesirable so that I modify the test further and insist upon the evening meal being a completely dry meal I have found that even the addition of watery fruit such as oranges or grapefruit occasionally will prevent a good concentration From the start of the test at 6 P M until the test is completed the patient does not have any fluids or foods The urine that is passed during the evening or during the night is discarded Fishberg has the patient pass a specimen the first thing in the morning at about 8 A M and label this specimen #1 The patient returns to bed and at 9 A M a second specimen is obtained Fishberg allows the patient to be up and about during the period between 9 and 10 A M and the patient voids at 10 A M into a third bottle There is therefore a period of sixteen hours during which the patient has no fluids According to Fishberg s results the specific gravity of at least one of the specimens should exceed 1 022 if the kidney function is normal Most commonly the specimen passed at 8 A M is the most concentrated specimen despite the persistent fluid restriction for several more hours Further modification of this test in my own practice consists of restricting fluids until at least 12 noon resulting in a period of 18 hours of fluid restriction and obtaining specimens at 8 10 and 12 Nevertheless even this change often does not give a concentration higher at 12 noon than at 8 A M

In the hypertension clinic at the Beth Israel Hospital, Boston we attempt

even more strict fluid restriction starting the test at 8 A M and running the test for 24 hours without any fluid The patient is allowed three dry meals during the day without any added fluid The urine is collected at two-hour intervals during the day and from 8 P M to 8 A M of the next day In this way we often secure a much higher concentration in individuals who did not concentrate satisfactorily by the Fishberg test One should note that an injection of pituitary solution may produce a markedly concentrated urine in a few hours[64] but this maneuver has not been adopted for clinical use

The concentration test is of such great value that unusual efforts should always be made to make certain the test has been carried out satisfactorily Sipping some fluid during the evening with medicine is a common mistake made by patients Another possible error in doing the concentration test occurs in patients in whom there may be slight or latent edema In these people restriction of fluids often will result in mobilization and excretion of the water from the edematous tissue so that the urine will remain unconcentrated during much of the test It is extremely wise always to repeat the concentration test on another day if the results are not satisfactory As already noted people with normal renal function should concentrate to a specific gravity of at least 1 022 and often go up to 1 030 Inability to concentrate above 1 020 on repeated satisfactory tests indicates definite damage of renal function Many patients complain somewhat of the thirst associated with carrying out the test and many hypertensive patients complain of headache nausea and weakness I agree completely with Fishberg that the concentration test is so simple and satisfactory that one can dispense in office practice with the phthalein output urea clearance test etc However when a patient is unable to concentrate well then it is necessary to proceed with these other renal function tests the most important next test being the determination of the blood urea nitrogen or nonprotein nitrogen

The study of the early hypertensive patient by concentration test reveals no abnormality these patients can concentrate to perfectly normal levels Repetition of such tests during the course of many years reveals that an individual may gradually lose some of his ability to concentrate this occurs in many of the patients with only moderate hypertension However the decrease in maximum concentrating figure is not great A patient who five years ago was able to concentrate to 1 03 may gradually show inability to reach that figure so that at the end of 6 or 7 years he is able to concentrate only to 1 022 or thereabouts However this patient still may have no clinical evidence of renal damage he usually has no nocturia polydipsia albuminuria and certainly has a normal blood chemistry However as ability to concentrate decreases a small number of hypertensive patients may begin also to excrete albumin and occasional granular casts The percentage of patients who develop true chronic vascular nephritis with constant albuminuria microscopic hematuria and marked lowering

of concentrating ability, probably is no more than 10 or 15 per cent of the tota number of hypertensive patients

In cases where there is definite impairment of concentrating power, the tests of renal function to be carried out are the 'phthalein and nonprotein nitrogen tests The use of the phenolsulfonepthalein test is apt to be somewhat unsatisfactory because the output of dye is dependent upon an adequate output of fluids Since in advanced cases of hypertension, where the 'phthalein test could be utilized more frequently, there is apt to be heart failure of varying degrees with latent or gross edema, failure to excrete fluid would result in failure to excrete the dye and give the wrong impression concerning renal function This same phenomenon occurs with the test for nonprotein nitrogen, which may be moderately elevated, if the individual is in any degree of heart failure Another source of error with the phthalein test is retention of the dye containing urine in atonic bladders or in bladders obstructed by prostate hypertrophy Both the 'phthalein and nonprotein nitrogen tests may be normal even in the presence of fixed low specific gravity due to the ability of the severely damaged kidneys to compensate by polyuria It should be noted that a borderline fasting nonprotein nitrogen of 39 to 42 mgm per 100 c c of blood should be viewed with the suspicion that the kidneys may be severely damaged especially in the presence of poor concentrating ability

Blood examinations in essential hypertension reveal no abnormality and even in those patients who develop marked degrees of chronic vascular nephritis, anemia may be slight or absent in contrast to cases of advanced chronic glomerular nephritis with hypertension The problem of polycythemia in hypertension constitutes in the author s experience, only a small group of cases, which really rarely enter into the differential diagnosis of essential hypertension and which also in the author s opinion represent a coincidental combination of two diseases one of which hypertension, is so common as to be associated necessarily, although only coincidentally with many rarer diseases

The basal metabolic determination in essential hypertension is usually normal or slightly elevated to top normal levels in the vast majority of cases However, there is a small group of cases of hypertension in whom there is a moderate elevation of the metabolism to levels up to even plus 50 or plus 60 per cent [65] In this group the patients have no enlargement of the thyroid gland There is no exophthalmos although there may be a stare, and neither iodine nor thyroidectomy change the level of the metabolism or the blood pressure On the other hand there are of course cases in whom there is a combination of true hyperthyroidism and essential hypertension

Blood circulation times are normal in patients who are free of congestive heart failure The blood volume acid base equilibrium blood cholesterol blood viscosity and blood proteins are within normal limits Various reports indicating

changes in these constituents in some groups of studied cases are open to the criticism that the group of patients studied were not young uncomplicated cases of the disease

Differential Diagnosis

The discovery of mild fluctuating arterial hypertension in a young person requires that the many causes of hypertension be considered and ruled out The most common cause of elevated blood pressure other than essential hyper tension is acute or chronic glomerulonephritis In acute nephritis the clinical picture is easily recognized since the individual usually has a history of preced ing acute infection such as sore throat with a subsequent latent period of several weeks following which commonly there are evidences of edema malaise fever and hematuria The degrees of these signs vary from extremely slight to very marked It is in the extremely slight somewhat latent cases of acute glomerulo nephritis that one finds the individual up and around with little or no com plaint In such cases the only abnormality found is in the examination of the urine Here you will find gross or microscopic hematuria mild to moderate al buminuria and usually normal concentrating ability In the vast majority of such patients with mild acute glomerulonephritis the blood pressure is normal In summary therefore the finding of mild hypertension together with albuminuria or hematuria with a preceding acute sore throat or other acute infection indicates strongly the diagnosis of acute glomerulonephritis in such cases the vast majority of patients become perfectly well and the hypertension does not persist The incidence of acute glomerulonephritis a a cause of early fluctuating hyperten sion is extremely small perhaps no more than 5 in 100 cases of mild fluctuating hypertension in young people Positive family histories of hypertension together with the presence of the hypertensive personality in the young subject of hyper tension argues strongly that his hypertension is due to the essential variety rather than any renal element

In young people with mild hypertension another even more rare condition must be considered and ruled out coarctation of the aorta In this condition a congenital narrowing of the transverse or descending aorta results in an in adequate blood flow to the body below thi narrowing According to the Gold blatt explanation such a narrowing results in a decrease in blood supply to the kidneys so that a humoral mechanism is set up similar to clamping the renal arteries As a result there is hypertension in the upper extremities while in the lower extremities palpable vessels are very faintly felt and blood pressure is much lower or not even determinable In this condition a systolic murmur is heard over the base of the heart and posteriorly and there is often observed a pulsation of the intercostal arteries above the point of constriction of the aorta

By x ray in cases advanced enough to produce hypertension one usually observes an irregularity or scalloping of the lower rib borders due to the constantly increased pulsation of the intercostal arteries acting as a collateral circulation causing an erosion of the lower border of the ribs The discovery of coarctation of the aorta has now become of practical importance since the surgical work of Gross indicates the great feasibility of successful surgical repair of this congenital lesion[66]

Unilateral or bilateral pyelonephritis in exceptional instances may cause hypertension The diagnosis here is made by first a past history of acute pyelitis together with the findings in the urine of white blood cells, albumin and frequently, bacteria Further investigation of the genitourinary tract results in the discovery of varying degrees of unilateral or bilateral hydronephrosis There are reported rare instances of the cure of hypertension in such cases by removal of the unilaterally damaged pyelonephritic kidney Such case reports, however, only rarely withstand critical analysis Bilateral pyelonephritis, however, obviously does not lend itself to nephrectomy The author and others feel that the finding of hypertension and chronic pyelonephritis is almost always a coincidental association[1]

Basophilic adenomas of the pituitary are another rare cause of hypertension[67] This rare picture is associated with painful obesity of face neck and trunk marked purplish striations of the subcutaneous tissue, hypertrichosis of face and trunk occasional kyphosis due to softening of the bones of the spine early amenorrhea or impotence and polycythemia occurring usually in young adults In these cases however, there is found occasionally an accompanying tumor of the adrenal gland and rarely is a pituitary tumor found, the etiology of the hypertension in such cases then remains uncertain The occasional report of radiation of the pituitary in such a case with a successful drop in blood pressure is extremely rare and difficult to evaluate

In both the younger and *older group of mild or moderate* hypertensive patients one must consider also the diagnosis of chronic glomerulonephritis which probably occurs about once in every 100 patients with chronic hypertension In this group there may or may not be a preceding history of an acute glomerulonephritis In addition to the possible past history one finds regularly the presence of albuminuria of mild to moderate degree The renal function as judged by concentration tests may be fairly well maintained for a long period of time with specific gravities of 1 022 or thereabouts obtained All other renal function tests may be normal for some years The hypertension in this condition however does not seem usually to progress so rapidly or so severely as in chronic vascular nephritis and hypertension may even be absent during the early years of the chronic stage of the disease The etiology of the hypertension in chronic and acute glomerulonephritis seems related somehow to the renal disease but the

exact relationship is completely unknown Certain it is that one may have pretty marked widespread chronic destruction of the kidneys such as with chronic pyelonephritis without any hypertension present It is also occasionally found that chronic glomerulonephritis of advanced degree may be present with little or no hypertension and only in the late stages of the disease may hypertension develop Nevertheless in this group of occasional instances it is necessary to recognize as significant a mild elevation of the blood pressure such as a blood pressure of 150/100 which sometimes is dismissed as a normal or unimportant reading Perhaps the consideration of these readings as abnormal would markedly decrease the already small number of cases of chronic glomerulonephritis in whom no hypertension is reported It should be noted again that since essential hypertension is an extremely common disease a certain number of patients who have chronic glomerulonephritis will be persons who would anyway have developed essential hypertension In such patients one would expect a much more severe form of hypertension due to the combination of hereditary vascular or vasomotor abnormality together with any possible humoral mechanism associated with the chronic kidney disease

The differential diagnosis between the malignant phase of essential hypertension and the advanced stages of chronic glomerulonephritis is difficult but frequently possible In both conditions there may be retinitis and a rapid course of the disease However various differential features exist In malignant hypertension there is less extensive edema of the retina and infrequent cotton wool snowbank exudates the discs are hyperemic and retina of normal color or hyperemic the retinal arterioles are sclerotic There is little or no general anemia Renal function may be completely normal or impaired later In chronic glomerulonephritis renal damage and insufficiency with anemia appear early and are the rule The anemia causes pale appearing discs and retina The retinal arterioles have only mild changes till very late Chronic glomerulonephritis usually occurs in earlier age groups 20 to 40 years than malignant hypertention 35 to 55 years

Perhaps one in a few hundred patients with hypertension has enlarged congenital polycystic kidneys as disclosed by palpation of the abdomen or by x ray In these cases also the disease is slowly progressive as the kidney tissue becomes more destroyed by the encroaching and enlarging cysts The mechanism of the hypertension here would seem to be on a renal basis

On rare occasions cortical or medullary tumors of the adrenal gland may cause acute paroxysms of marked hypertension associated with rapid pulse pounding headache and pallor[65] In these cases the blood pressure drops to a normal level between the crises or at least drops to much lower levels The blood pressure during the crisis may be marked and damaging enough to cause a cerebral hemorrhage and yet a subsequent examination after the paroxysm usually discloses a normal blood pressure It is also to be noted that gross tumors

of the adrenal gland may be found frequently in patients with hypertension in whom there are no symptoms suggestive of the syndrome of this condition Smithwick found 6 such unrelated adrenal tumors during the operation of sympathectomy in 156 hypertensive patients[69] In such cases it would seem that the adrenal tumor had no direct or indirect relationship to the hypertension which is of the essential type Removal of the adrenal tumor in the typical case of paroxysmal hypertension results in cure of the hypertension providing the tumor is not of the malignant variety If it is malignant and there are metastases the metastatic lesions may produce a recurrence of the hypertension and accompanying symptoms

A rare case of brain tumor if situated in the proper position to cause marked interference with cerebral circulation and particularly through the vasomotor areas of the brain may conceivably result in hypertension This type of hypertension is similar to the experimental hypertension produced by tying off cerebral arteries and causing cerebral anoxemia[5] However it should be emphasized that this type of hypertension also is extremely rare The changes in the optic discs of malignant hypertension and chronic glomerulonephritis may closely simulate those found in brain tumor

The existence of hypertension during pregnancy always causes difficulty in differential diagnosis If one is acquainted with the patient prior to pregnancy or during the extremely early stages of pregnancy it is easy to know whether the patient had preexisting chronic glomerulonephritis The discovery of hypertension and albuminuria in the first weeks or months of pregnancy should bring up the question of the differential problem of chronic glomerulonephritis Enlargement of the heart by percussion or 7 ft heart film or the presence of thickened peripheral arteries suggests a more long standing cause for the hypertension rather than the pregnancy In such cases of preexisting chronic glomerulonephritis pregnancy usually is a serious aggravating factor Early in pregnancy such a patient will complain of many symptoms such as weakness headaches and difficulties in vision In this stage there already is marked evidence of renal function impairment The urine is typical of chronic glomerulonephritis and the nonprotein nitrogen of the blood may be elevated Observation of the patient during the early weeks and months of pregnancy discloses that the blood pressure is rising and that the patient is obviously becoming more ill Fetal mortality is extremely high and the best treatment is to empty the uterus Despite the usual seriousness of preexisting essential hypertension or chronic glomerulonephritis there are a number of such patients who become pregnant and encounter no complications or significant aggravation of their preexisting disease process However it is clear that such patients with chronic glomerulonephritis should not become pregnant because there is a high fetal mortality, even if the disease process itself occasionally is not significantly aggravated Mild hyper

tensives however, may if their renal function still is good become pregnant with a moderate possibility of going through pregnancy with delivery of a normal baby providing they understand that there is some degree of risk and that pregnancy may have to be terminated

Essential hypertension in pregnant women usually is of a mild variety because the disease usually is in the extremely early fluctuating stages Our best knowledge at this time suggests that pregnancy may be a precipitant of temporary essential hypertension in many of the persons who later will have the full blown disease This is evidenced by many studies of families of such patients and also by follow up studies[70] In most such cases the blood pressure promptly returns to or near to normal after delivery However a careful study of such patients between pregnancies has shown the author that these people still retain the vasomotor pressor responses of hypertensives and their initial readings on examinations are frequently though only momentarily elevated

The so-called degenerative kidneys of pregnancy are associated frequently with moderate to severe degrees of hypertension In this condition as distinguished from chronic glomerulonephritis and essential hypertension the hypertension usually develops during the last trimester of pregnancy There is mild to marked degrees of albuminuria gain in weight due to latent edema followed soon by obvious edema and occasionally edema of the retina In this condition renal function usually is good as distinguished from chronic glomerulonephritis Termination of pregnancy results in the complete disappearance of the hypertension and renal signs The presence of hypertension in the so-called degenerative kidney of pregnancy is a bad sign and is a good reason for terminating the pregnancy

A true toxemia of pregnancy is so-called eclampsia and occurs in patients who already show the signs of the degenerative kidney of pregnancy It therefore occurs also during the last third of pregnancy This condition always is associated with hypertension of severe degree The hypertension is associated with severe headache vomiting difficulties in vision and eventually serious convulsions The cerebral symptoms in such cases are considered to be of similar origin to the hypertensive encephalopathy found in other conditions

The presence of hypertension in urinary obstruction due to an enlarged prostate or other obstructing condition is common However in almost all of these cases we are dealing with essential hypertension associated with the genitourinary condition A carefully studied occasional case will disclose however that the blood pressure had been fairly constantly elevated prior to genitourinary treatment and dropped close to normal following treatment In such occasional cases a direct relationship must be considered and is probably similar to the experimental phenomena showing that such obstruction may produce hypertension in animals

Finally numerous rare and some rather dubious causes of arterial hypertension may be mentioned. Involvement of the kidneys by any process or processes obstructive to the genitourinary tract are considered by some observers as an occasional cause of hypertension. However, here again it is a difficult problem to prove such etiological relationship. A disease that is as common as essential hypertension is bound to be found frequently and consistently in the presence of every less common or rare disease.

Classifications of hypertension have been made in which almost every known disease of the kidneys and genitourinary tract has been listed as a cause of hypertension with the explanation that such disease processes produce an abnormality of the renal circulation and, therefore, a Goldblatt or Page type of hypertension. Thus, for example, are listed involvement of the renal arteries by periarteritis nodosa, thrombo-angiitis obliterans, lupus erythematosus, embolism, thrombosis, etc. and involvement of the renal parenchyma by infarction, renal stones, amyloidosis, etc. among the many known renal pathological processes. A rare case with such apparent etiological relationship has actually been reported following renal infarct, arteriosclerotic occlusion of the main renal arteries, etc.[71]

Hyperthyroidism and complete heart block may each produce systolic hypertension as a result of an increase in the cardiac output.

There is no satisfactory evidence for the existence of a menopausal hypertension unless one means that momentary vasomotor reactions produce momentary transient changes in blood pressure. The usual finding is the menopausal vasomotor reaction aggravating a preexisting or beginning true essential hypertension.

In summary, however, the two types of hypertension most frequently encountered are hypertension due to nephritis and by far the most common essential hypertension.

Treatment

It is necessary to view a patient as a whole human being when treating him for any disease. This same plan holds for essential hypertension. It must be recognized that we are dealing in essential hypertension with an individual who has an hereditary tendency to the disease and who is born with or at least in very early life begins to evidence certain physical and emotional reactions to his environment which we term the hypertensive personality. Such a personality results in the development of various psychoneurotic symptoms in many cases. Later the disease process itself produces symptoms and throughout this period we are dealing with an elevation in blood pressure which gradually damages the blood vessels and consequently vital viscera. All these individual aspects have to be considered in each patient in order to discuss adequately the treatment of essential hypertension.

It is best to divide such treatment into the therapy of the symptoms and the therapy of the blood pressure elevation itself Finally one has to consider the therapy of the impaired function of various organs damaged by the disease

Interpretation of Symptomatic Relief

The physician in practice is faced with a constantly increasing literature on the treatment of essential hypertension In 1930 analysis of the literature by the author[43] disclosed that the successful treatment of essential hypertension by the use of many different drugs and methods of treatment had been reported at least 200 times in the preceding decade Similarly the period since 1930 is almost a carbon copy of the past However the constant employment of new drugs and methods which usually are discarded after a brief popularity indicates that none of these methods are actually specific The physician in practice must constantly bear in mind therefore that all these papers have certain common fallacies that are responsible for these numerous although short lived claims of success These fallacies concern the interpretation of therapeutic results Analyses of most papers that appear on the subject of the treatment of essential hypertension indicate that in practically every report complete or partial symptomatic relief is mentioned A moderate reduction of blood pressure also is reported and occasionally marked reduction The degree of symptomatic relief however is generally much greater than the degree of blood pressure reduction and as a rule is frequently out of all proportion to the amount of reduction in blood pressure

Marked symptomatic relief sometimes is reported without any reduction in blood pressure of the patients studied Finally most papers in the past have seldom reported complete failure If these papers are correct it must be concluded that the symptoms associated with essential hypertension which the various writers have treated are easily relieved It must also be concluded that they are relieved more easily than the blood pressure is lowered and that the relief may be obtained by the use of any of numerous drugs and methods It is not probable however that each of these drugs has a specific action It is more reasonable to believe that there is a common and specific factor associated with the administration of most of these drugs The author feels that this common element is the enthusiastic giving or doing of something to a patient it is treatment regardless of its nature

The effect of such treatment was studied by the author in a group of 40 patients Patients whose symptoms seemed to be due to secondary demonstrable changes of the vascular system were excluded During such a study a complete history was taken symptoms again recorded physical examination again made although most of the patients had been followed for months or years In this

way the patients were impressed at once with the new interest manifested in them by the author The next step was to prescribe seriously and enthusiastically 10 drops of dilute hydrochloric acid to be taken in a half glass of water 15 minutes before meals 3 times a day Dilute hydrochloric acid was selected because it certainly could not be credited with any specific power in the treatment of essential hypertension and yet in such dosage it still possesses an impressive taste The patients were ambulatory and were seen at weekly intervals and received no other treatment during this investigation They were treated over periods of 1 week to 4 months

The amazing finding was that 33 of the 40 patients showed definite improvement giving 82 per cent success although success was disregarded in those in whom only slight relief was obtained The symptoms relieved were of great variety and multiplicity insomnia, headache nervousness, fatigue weakness loss of appetite and dizziness were those most commonly relieved In addition to the relief of these individual symptoms there was encountered almost regularly a marked general improvement The patients appeared happier and said that they had more ambition and energy A general sense of wellbeing developed In some patients decreasing the dose seemed to slow up improvement and in a few instances this placebo effect was striking Like most drugs and methods of therapy the present treatment had 'untoward effects in 3 patients

As a result of such study, which may be repeated by any man in practice, one would have to conclude that dilute hydrochloric acid or ' treatment ', would have to be added to the armamentarium of the physician The query naturally occurs as to the mechanism of the symptomatic relief obtained by so many drugs The shortness of breath of heart disease or the pain of pleurisy do not admit of such varying yet successful therapy There is no other disease excluding psychoneurosis in which the symptoms are influenced so easily and so variously Only one explanation for these universally successful results in the treatment of symptoms in hypertension appears at all possible namely that the symptoms associated with essential hypertension are so frequently of psychic origin that they may be relieved by suggestion inherent in any drug or method utilized by the physician When this study is analyzed by psychiatrists they prefer to interpret this nonspecific treatment and improvement by the psychiatric term the transference effect

Treatment of Psychoneurotic Symptoms

Therefore it is mandatory that physicians who treat the symptoms of patients with essential hypertension recognize that the early symptoms of essential hypertension are of psychoneurotic origin Such psychoneurotic symptoms how

ever beginning in the early life of hypertensive patients recur throughout life regardless of the fact that organic symptoms may develop also The physician must critically analyze every new report concerning the treatment of the symptoms of essential hypertension in the above light He must determine carefully whether such reports have taken into account treatment which has just been described in reporting on dilute hydrochloric acid before concluding that the reported drug is valuable

In other words it is always necessary to try a placebo for 2 or 3 weeks of close observation in such patients before prescribing the new drug for which claims are made The physician should evince as much or as little enthusiasm for the placebo as he does for the new drug Such a procedure is perfectly proper in private practice since as yet we have no medical treatment that is a specific for such psychoneurotic symptoms

Until such time that a specific drug is discovered for the treatment of the symptoms of psychoneuroses and a specific drug is discovered that will really change personality, the psychoneurotic symptoms of essential hypertension should be treated like psychoneurotic symptoms in general The treatment should consist of psychotherapy and the use of sedatives For general practice psychotherapy does not require complex psychoanalysis but merely a careful inquiry into the emotional problems of the patient Upon finding the causative emotional problem that preceded the development of the symptoms it is necessary to show the patient adequately that his symptoms are due to these problems rather than to the blood pressure elevation itself An attempt then to make the patient change his poor reaction or adjustment to these problems will at once start him if he is at all cooperative on the road to recovery from his symptoms

Sedative therapy in patients with this group of symptoms should accompany psychotherapy The simple sedatives are the best In the case of patients who become fatigued from night after night of broken sleep adequate doses of phenobarbital 0 1 to 0 2 gm (gr 1 5 to 3) or chloral hydrate 0 65 to 1 3 gm (gr 10 to 20) or amytal 0 1 to 0 2 gm (gr 1 5 to 3) are given night after night until adequate sleep results in a return of pep and vigor In the daytime a simple sedative such as elixir sodium bromide one teaspoonful two to three times a day after meals will make the day more bearable The complaints of headache fatigue irritability etc also will improve markedly It should always be borne in mind that one of the emotional bases for the psychoneurotic symptoms in hypertension is the fear of the disease itself the fear of a shock or heart attack Reassurance concerning the good general state even although not absolutely true is also proper therapy since by keeping the patient s psychic state calm it must reasonably follow that his organic state is definitely aided

Treatment of Vasospastic Symptoms

Chief of the vasospastic symptoms are headache and dizziness, the former being by far the most common In addition symptoms referable to any part of the body are to be expected, since wherever arterioles may go into spasm there one may have the symptoms of temporary ischemia Sometimes the severe prolonged headaches of vasospastic origin respond to large doses of sedative as already outlined or to periods of rest or vacation Such sedatives must be used over long periods of time Sometimes these headaches respond to the analgesic group of drugs in which aspirin, caffeine codeine and acetphenetedin are given separately or in varying compound pills However, the drug most useful for the relief of these severe recurring headaches and dizziness is potassium thiocyanate The dosage and method of use of this valuable potent drug will be outlined later on under the treatment of the blood pressure elevation itself

In those cases which do not respond to the thiocyanates intramuscular injection of magnesium sulphate may be tried and occasionally is successful Here one may use the ampoules containing the 50 per cent solution giving several centimeters every 2 or 3 hours for about 6 doses In some patients in whom intense headache is not relieved by the above methods lumbar puncture occasionally will afford relief In such patients it is frequently, but not necessarily, found that the spinal fluid pressure is somewhat elevated Finally it should be noted that occasional cases with severe headaches waking them in the early hours of the morning may be benefited by asking the patient to sleep in a semi propped up position with the head elevated

Treatment of Organic Symptoms

The outstanding organic symptoms are those which indicate impairment of cardiac or cerebral or renal function Shortness of breath is one of the earliest symptoms of impairment of cardiac muscle function Such shortness of breath at first is noted by the patient when he climbs stairs or inclines Since many of these patients are obese the obesity frequently is blamed for the breathing distress Even without shortness of breath excessive weight should be reduced to a normal level on the grounds of general common sense Reduction of weight certainly relieves a burden on even the normal heart In the case of obese patients with cardiac enlargement and shortness of breath weight reduction likewise will operate in a successful manner The speed of progress of the shortness of breath is an extremely variable and individual matter so that in one patient the shortness of breath may only gradually progress during the course of 4 to 5 or 6 years while commonly the entire full blown clinical picture of congestive heart failure may develop in some patients in a few months

The cause of shortness of breath in a patient with a heart of normal size by x ray must be sought in a condition other than essential hypertension In other words by the time true shortness of breath develops the patient with hypertension already has definite heart enlargement The sensitivity of some people to mild shortness of breath is not great when the cardiac hypertrophy is of slow progress so that the patient adapts himself to the light increasing discomfort and frequently does not complain of it or seek medical attention because of it As a result one often sees patients in whom the first evidence of cardiac difficulty is a full blown attack of cardiac asthma or pulmonary edema Careful history in such cases will indicate however that progressive shortness of breath has existed for several month or years The treatment of such shortness of breath due to enlargement of the heart by long continued elevation of the blood pressure in essential hypertension is the same as shortness of breath due to any cardiac disease When the shortness of breath is merely on exertion and there is no evidence of congestion in the lungs liver or peripheral tissues full digitalization during the course of a week weight reduction and a decrease in those activities which produce shortness of breath should be the chief treatment One may add to these the use of aminophylline or theobromine These drugs however are used not for their effect on blood pressure itself but rather to effect improvement in the coronary circulation of the heart muscle itself As a matter of fact aminophylline and theobromine have no discernible effect upon the blood pressure itself If shortness of breath is extreme then absolute bed rest is indicated for periods of 10 days to 3 weeks depending upon the extent of the distress When hypertensive heart disease progresses to the stage of right sided heart failure with peripheral edema constant pulmonary rales and enlargement of the liver the use of mercurial diuretics is indicated These diuretics such as mercupurin and salyrgan will often produce remarkable improvement These mercurials not only are of value when there is obvious peripheral edema but in the patients with chronic heart failure without edema In these patients in whom the clinical picture is one of almost pure orthopnea and dyspnea the mercurial diuretics still will have a very striking effect and when repeated at frequent often weekly intervals they may keep such patients comfortable for months or years The added use of ammonium chloride for 48 hours before the mercurial injection results frequently in added diuresis The recent production of the same mercurial preparation for oral use has been a real step forward By such means it is possible to decrease and often to omit entirely the number of intramuscular or intravenous injections and there is thereby a great saving of pain and money to the patient who must be treated for often as long as 3 or 4 years The use of low sodium diets for congestive heart failure permits a greater intake of fluids without edema formation

The development of true nocturia is a symptom of advanced renal function

impairment However, the specific gravity by concentration test may still be as high as 1 018 to 1 022 in the presence of frequent nocturia The presence of nocturia with some decrease in concentrating ability is a common finding in advanced hypertension but does not mean that such a patient is going to die of uremia It is by far more common for such patients to die of a cerebral or cardiac complication The treatment of renal function impairment is much less satisfactory than that of the heart There is no specific drug that actually improves renal function The sole plan in treatment is to decrease the work of the remaining renal units and to decrease within maintenance bounds the ingestion of excessive proteins whose end products are excreted by the kidneys However the presence of mild to moderate albuminuria indicates the essential need of maintaining adequate protein intake, so that the level of the blood proteins do not drop Such adequate protein intake is possible so long as the kidneys do not go into renal failure with resultant retention of the nonprotein nitrogen and other end products ordinarily excreted When this does occur, one is forced to decrease the protein intake to whatever amount is necessary to lower the elevated blood chemical end products It should be noted that hematuria, either gross or most commonly microscopic occurs extremely frequently in patients with impairment of renal function due to essential hypertension The pathological process which produces renal function impairment in essential hypertension, is called chronic vascular nephritis Nature teaches the patient with chronic vascular nephritis or with any other form of renal function impairment to drink an adequate amount of fluids, so that a compensatory polyuria will maintain an adequate excretion of the end products of protein metabolism In the common combination of chronic congestive heart failure and chronic renal function impairment it becomes extremely essential still to maintain an adequate supply of fluids for the maintenance of whatever remaining kidney function exists Such a combination seems best treated by the rigid restriction of salt so that an adequate fluid intake may be taken without deposition of edema fluid from the heart failure

The use of mercurial diuretics is contraindicated in the presence of renal failure Here again however one must attemp clearly to distinguish between the temporary depression of renal function by cardiac weakness with renal congestion and true renal function impairment In the former case a lack of adequate fluid excretion results in a low phthalein output mild to moderate elevation of the nonprotein nitrogen but usually there is excreted a urine of good specific gravity In the presence of true renal failure, however, cardiac failure produces even more marked elevation in the nonprotein nitrogen of the blood, decrease in the 'pthalein dye output and a pale urine of low specific gravity On the other hand cardiac failure and circulatory congestion of the kidneys will not produce extreme elevation of the nonprotein nitrogen and usually no extreme depression of the 'pthalein output in the presence of normal kidneys Where such extremes

are found one may pretty well conclude that impairment of renal function preceded the cardiac failure

The anemia which may develop as a result of renal function impairment in essential hypertension usually is slight yet rarely it may be very marked It does not respond particularly to maximum doses of liver extract or iron Blood transfusions are palliative in such cases but should be given with care to prevent reactions

In the treatment of chronic vascular nephritis one should also keep in mind the fact that constant damage is being produced by the vasoconstriction of the vessels supplying the glomeruli and tubules If one can relieve such vasoconstriction then it would seem obvious that progress of the renal function impairment would be slowed up Sympathectomy would seem to offer such a possibility as will be discussed on a later page

When the symptoms and signs of true renal insufficiency develop the treatment becomes even more obviously palliative In such situations replacement of fluid and salt by small saline intravenous or subcutaneous injections becomes necessary This will in many cases temporarily stimulate the output of urine Transfusions for anemia calcium chloride for the tetany of uremia and bicarbonate of soda for acidosis are some of the maneuvers that must be carried out in this advanced stage of chronic vascular nephritis

Treatment of the Elevated Blood Pressure Itself

It has been indicated already that it is best to separate the treatment of the symptoms from the treatment of the elevated blood pressure itself with its associated arteriolar constriction because one may so easily relieve many of the symptoms associated with essential hypertension by simple non specific means of suggestion and psychotherapy It is essential therefore to view the problem of the treatment of the elevated blood pressure itself separately in order to prevent as much as possible misinterpretation of therapeutic results It is best at this point to describe in detail the various factors which unrecognized or frequently disregarded seem to lead to incorrect conclusions regarding the reduction of the blood pressure in essential hypertension

The individual fallacies appear to spring from a source of error provision against which is important in any investigation or therapeutic evaluation the inadequate studies of controls Almost all studies on the treatment of essential hypertension have lacked sufficiently long and carefully regulated periods of observation prior to the administration of therapy This inadequate control period usually results from the failure to recognize just what factors to control The control of the various factors to be discussed applies to general practice quite as much as to research in hypertension clinics

impairment However, the specific gravity by concentration test may still be as high as 1 018 to 1 022 in the presence of frequent nocturia The presence of nocturia with some decrease in concentrating ability is a common finding in advanced hypertension but does not mean that such a patient is going to die of uremia It is by far more common for such patients to die of a cerebral or cardiac complication The treatment of renal function impairment is much less satisfactory than that of the heart There is no specific drug that actually improves renal function The sole plan in treatment is to decrease the work of the remaining renal units and to decrease within maintenance bounds the ingestion of excessive proteins, whose end products are excreted by the kidneys However the presence of mild to moderate albuminuria indicates the essential need of maintaining adequate protein intake so that the level of the blood proteins do not drop Such adequate protein intake is possible so long as the kidneys do not go into renal failure with resultant retention of the nonprotein nitrogen and other end products ordinarily excreted When this does occur, one is forced to decrease the protein intake to whatever amount is necessary to lower the elevated blood chemical end products It should be noted that hematuria either gross or most commonly microscopic occurs extremely frequently in patients with impairment of renal function due to essential hypertension The pathological process which produces renal function impairment in essential hypertension is called chronic vascular nephritis Nature teaches the patient with chronic vascular nephritis or with any other form of renal function impairment to drink an adequate amount of fluids so that a compensatory polyuria will maintain an adequate excretion of the end products of protein metabolism In the common combination of chronic congestive heart failure and chronic renal function impairment it becomes extremely essential still to maintain an adequate supply of fluids for the maintenance of whatever remaining kidney function exists Such a combination seems best treated by the rigid restriction of salt, so that an adequate fluid intake may be taken without deposition of edema fluid from the heart failure

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In hospitalized patients most physicians secure the average blood pressure by keeping the patient in bed for perhaps 1 to 2 weeks before starting treatment During this time the level of blood pressure frequently may drop considerably below that of the ambulatory period of observation The burden of proof rests on these physicians to show that the blood pressure would not continue to drop without treatment after a 2 week control period in bed In reality it has been shown that in many patients drops in blood pressure do not appear until after 2 weeks or more in bed

Another present day error of great proportion has been the poorly controlled preoperative studies of hypertensives in whom sympathectomy is being planned In such cases many surgeons have followed a routine which consists of 3 or 4 days office or hospital observation Here we are dealing with the problem of trying to secure blood pressure levels before operation which are subsequently used to compare with the postoperative blood pressure levels The difference in these levels then is cited as the actual improvement from operation This is an intensely gross fallacy The fallacy arises from the well known but ignored fact that when a patient with essential hypertension enters an office or hospital with the idea of being studied for his suitability for sympathectomy or for any operation he is naturally in his most intensely nervous state Here is being decided the question of what he believes are serious operations for what he knows is a serious disease otherwise operations would not have been considered It follows quite simply that levels obtained during such a 3 or 4-day period are at their extreme and their worst Repetition of these tests even a few days before operation will still be done in patients who are in an extremely agitated emotional state Postoperative repetition of these tests months or a year after operation i done then in patients who are in an entirely different state of mind The comparison then of these abnormally elevated preoperative pressure levels with postoperative levels will give the impression that the improvement has been tremendous whereas it may be none or only slight to moderate It follows therefore that in such cases the true preoperative levels must be based on careful observation over a long period made before the problem of sympathectomy has been seriously injected into the patient s thoughts

Another important uncontrolled factor in securing the average blood pressure before any treatment is that the visits to the office or clinic are much more frequent during the period that a special new drug is being studied than during the so-called control period of ordinary office observation and visits I have found that there is in many cases a rather definite relationship between the frequency of visits per se and the height of the blood pressure that is to say the more frequent the visits the lower the blood pressure within limits[64] Such frequency of visits seems to operate on the blood pressure as follows the patient with essential hypertension eems to be excessively influenced by the enthusiasm

The lability of blood pressure in essential hypertension has been discussed already under the heading, Evolution of the Disease It was emphasized that there is a continual variation of the blood pressure in essential hypertension It is usually lower in the morning than in the evening and may even drop to normal during sleep It is lower after a rest period than when taken without rest It is lower in a quiet room than in a noisy room The mere entrance of another person into a room, where the blood pressure is being taken frequently will cause a rise in blood pressure The sudden preoccupation of a patient with a disturbing thought similarly may elevate readings The diastolic blood pressure varies by percentage as much as the systolic Although many physicians appreciate this instability of the blood pressure level they often overlook its great influence on their therapeutic results A casual observer will be misled into thinking that it is a meaningless variation whereas in fact lability is in direct relation to all changes in the environmental physical and psychic states Therefore everything that affects the patient s environment, body and mind must be controlled as much as possible when one is evaluating the results of attempts to lower the blood pressure

Determination of the Average Blood Pressure Level before Treatment — In evaluating the results of their attempts to lower the blood pressure many physicians use as control figures the average blood pressure they obtain before their special therapy is instituted In ambulatory patients the average usually is obtained from the blood pressure readings taken during the months or years of past observation in the office or clinic This would seem to be an accurate control procedure, but actually often it provides a loophole in an otherwise well planned study In general this method is inadequate because the patient's past blood pressure readings to be averaged may have been, and usually are taken under conditions different from those during the investigative period

The most important of these different conditions before and during treatment is that the control readings previous to treatment usually are taken without rest periods while the readings during the studies usually are taken after rest periods The blood pressure observation prior to receiving treatment is in consequence an uncontrolled one because it is done during routine office or outpatient practice usually without future studies in mind In the office or clinic blood pressure readings after the initial visit usually are taken without much ado or plan before talking with the patient during talk with the patient or during an examination To compare such random past readings with those taken after 10 to 20 minute rest periods is not justifiable because in so doing the lability of the blood pressure is disregarded The hypertensive patients often will have a systolic drop of from 30 to 100 mm Hg on resting from 10 to 20 minutes it is not all therapeutic effect, therefore when the readings of the blood pressure taken after rest periods during drug administration show much lower figures than the control figures without a rest period

perature pulse rate or give himself insulin or penicillin injections There are some patients who naturally would become undesirably up et by any maneuver requiring self observation Such people are best not included in such studies or in such cases some member of the household is taught how to carry out the particular observation desired in thi case the determination of the blood pres sure levels We have utilized thi method a explained under the previous head ing Evolution of the Disease By this method it was first observed that the blood pres ure in untreated patients wi h essential hyperten ion often is con siderably lower in the home than in the office or clinic[27] The continuation of this method durin and after trea ment permitted an even better evaluation of the effects of therapy than all of the above described method of control In general the home blood pressure studies are of value in studying the effect of any therapy which has only small al hough defini e effects on the blood pressure since it permits the construction of a curve of blood pressure based on a large number of daily reading It is pos ible therefore to evaluate drops in blood pressure whether of only 10 to 20 mm Hg systolic whereas if scattered office readings alone are used uch decreases are not brought out or cannot be evaluated The use of the home blood pressure method also permits the satisfactory evalua tion of drug throu h the use of a small number of cases It is apparent that results in a dozen cases studied by this method give more conclusive informa tion than results in a much larger series studied by means of occasional weekly readings Finally the home blood pressure method removes the pressor effect of the physician s presence We have already observed that the result of treatment is masked frequently by considering only the office or clinic blood pressure read ings This is due to the fact that the doctor particularly and the office it elf to some extent is a form of standard pressor stimulus similar to breath holding or cold The operation of this stimulus overcomes the hypotensive effect of drugs or operation in many cases With the removal or omission of this stimulus and the determination of the blood pressure at home by a member of the household or the patient himself the true hypotensive effect from therapy becomes evident The physician also should realize clearly that a patient with essential hyperten sion can no more become non reactive to the physician by repeated visits over period of even years than he can become non reactive to repeated pressor tests of cold or breath holding

Finally in this detailed discussion of control study of blood pressure before therapy it is essential to use a placebo in all patients in the same dosage enthu siasm and for the same length of time as one utilizes in the prescription of the drug to be studied and evaluated In our own studies at the Beth Israel Hospital Hypertension Clinic the author uses the following system There is maintained a flow of untreated patients with essential hypertension who come month after month and who remain the reservoir from which now and then are taken patients

pessimism or indifference of his physician which is reflected in the level of his blood pressure Such enthusiasm operates first through its effect on the hypertensive personality and subsequently by means of the blood pressure lability To understand this clearly one should picture the medical life of the average hypertensive patient He knows too well the possibility of having a cerebral hemorrhage and in his anxious quest of cure wanders to many clinics or doctors Especially in clinics too often a busy physician after a few brief questions hastily writes a prescription, for example, of potassium iodide, and in a manner, that the apprehensive patient regards as indicative of a lack of interest in his case tells him to return in a few weeks or months At the next visit to the crowded clinic frequently a different physician sees him rapidly takes his blood pressure and either advises continuing the medicine or orders for example, a low salt or low protein diet So it continues during subsequent visits with the patient still feeling anxious about his high blood pressure and dubious as to his future Then a different physician appears who with faith or hope in some new drug begins to treat the patient carefully seriously and optimistically The patient now returns 2 to 3 times a week and is questioned carefully examined and advised The patient naturally becomes interested and encouraged by the eager attempts to cure the disease which he believes otherwise may cause his death at any moment He responds as most people would he becomes happier, more contented and less excitable The result is definite there is subjective improvement and frequently a fall in blood pressure, but the investigator usually fails to separate this effect from any effect that might be due to the drug The effect of frequency of visits alone without drug therapy is a similar drop of blood pressure due to the greater calmness resulting from repetition of visits

Finally most pre treatment observations are not of adequate length of time Aside from controlling the frequency of visits and the matter of rest periods the pre treatment period before introducing a drug must in itself be sufficiently long for only by long observation can one get a true picture of the untreated lability in the individual case The natural lability of the individual's blood pressure is due to many uncontrollable changes such as weather emotional upsets catamenia and the natural course of the disease Adequate length of pre treatment observations will result in showing that all cases have fairly good ranges of fluctuation

The home blood pressure determinations by patients with essential hypertension have been employed by the author for the purpose of further evaluating the patient's blood pressure levels and the effect of treatment It was originally utilized for the study of clinic patients However, it certainly may and should be utilized by physicians in the private practice of medicine The same attitude should be adopted towards the use of the home blood pressure method as is adopted by the physician when he teaches the patient how to take his own tem

there has been a restoration of thiocyanate to its rightful place in the treatment of essential hypertension Nevertheless again at the start of discussing this drug it should be emphasized that it must be administered under careful observation

The chief contraindication to the use of the drug is the presence of renal function impairment Where the kidneys cannot excrete well the normal products of metabolism they likewise will not excrete the drug adequately so that it will accumulate rapidly in the blood with toxic result A review of the literature of thiocyanate treatment reveals that 8 deaths during therapy have been reported associated with the use of this drug Analysis of the reports of the fatal cases indicates that 5 of the 8 reported patients had advanced renal function impairment before treatment In the remaining 3 or 4 cases the reports themselves of the cases are so inadequate that one cannot determine the true status of renal function It becomes obvious therefore that death from thiocyanate will occur chiefly if not wholly in those patients who have impairment of the excretory power of renal function The first prerequisite therefore in the use of the drug is the determination of the patient s renal function This should be done by the method of renal concentration test already described A satisfactory patient for thiocyanate therapy should be able to concentrate his urine to a specific gravity of at least 1 022 If he does not show such concentration after repetition of the fluid restriction test then it is wise not to use the drug or at least to use it with the greatest of caution and the smallest of doses I have found for example that a 0 2 gm (gr 3) tablet given as infrequently as every other day for one week total dose of 0 6 gm (gr 9) causes a rise in blood level to 8 mgm in a patient who could not concentrate the specific gravity of her urine above 1 018 and who died of uremia some months later Failure to recognize the severe renal function impairment in this case and the incorrect use of a larger standard dose would have resulted in extremely high blood thiocyanate levels and consequent toxicity The same might have occurred in this patient if for example bromides were given in large doses

Having secured evidence of good renal function the drug may be used in hypertensive patients if they do not have heart failure In this situation the drug would distribute itself as in all cases throughout the tissues of the body and also in any edema fluid present It should be noted that the thiocyanates when absorbed into the body are normally distributed throughout all of the intercellular fluids and as a matter of fact the drug is used at times to measure the total volume of intercellular fluids If the amount of intercellular fluid is abnormally increased as with edema from any cause then the percentage of drug in the blood is decreased with any given dose Therefore much larger doses of the drug would be required to maintain the therapeutic blood levels and the risk of sudden variations in concentration might be great On the whole therefore the

for the evaluation of various drugs or other kind of treatment During this period of non treatment the patient is given placebos in different colors and doses so that he feels he is getting treatment Amazingly enough such treatment frequently is found effective, as we have already explained During such visits to the clinic the patient is taken at each visit into a quiet room, and the blood pressure is taken at once on sitting down and again on several other occasions during a twenty minute rest period These individual visits then give us a reasonably well controlled placebo treated observation of blood pressure When we plan the trial of a new drug we choose a certain number of reasonably cooperative patients and commence to see these patients at weekly intervals still using placebo treatment Where possible we then also begin to secure home blood pressure readings so that we have not only controlled clinic observations but also home observations After at least 6 to 8 weeks of such control clinic and home observations then we introduce the new drug or method to be studied and then one is in a clear position to determine whether there has been any therapeutic effect In the case of patients who are being subjected to sympathectomy, an attempt is made as often as possible to secure clinic and home observations for at least a few months before the patient is seriously advised to have sympathectomy

Drugs and Methods for Lowering the Elevated Blood Pressure — Patients with very mild elevation of the blood pressure with frequent drops to normal and who still are young and without any evident organic changes and especially without symptoms are treated best with the simple sedatives in moderate dosage enough to keep them relaxed and calm

When the blood pressure reaches more persistent levels such as 190/110 and when there are severe headaches then it is necessary to consider a more active means of treatment Only two practical methods are now available for lowering to any extent the blood pressure itself, the use of potassium thiocyanate and the operation of sympathectomy

POTASSIUM THIOCYANATE The thiocyanates, and whether one uses the potassium sodium or ammonium salt does not matter will often lower the blood pressure level to an important extent and will improve strikingly the severe headaches of hypertension The thiocyanates however, have gone through many periods of disrepute In 1928 the author studied the use of potassium thiocyanate in the treatment of essential hypertension and at that time found that it did have a hypotensive effect but that the effect was almost always associated with distressing untoward reactions The author at that time concluded it was an impractical drug to use[73] However a great advance in the use of this drug was made when it was shown that by determining the blood thiocyanate level at regular intervals during the administration of the drug it was perfectly feasible to use the drug and avoid disturbing toxic reactions[74] Since then, therefore,

patients blood levels may remain around 3 or 4 mgm despite the use of as much as 0 2 gm 4 times a day week after week It would not seem reasonable to feel that a drug which is absorbed into the body and is distributed into all the intercellular fluid should have that much variation in its levels Such variations in blood levels would indicate either that the drug is excreted more rapidly at times or that the intercellular fluid increases 3 or 4 times its normal amount or finally that the drug is not completely absorbed We know that intercellular fluid in people without evidence of edema normally will not change markedly It is also known that the rate of excretion through the kidneys of thiocyanate does not change markedly day by day The possibility of lack of absorption is the only chief remaining factor Patients who took such large doses of the drug without building up a therapeutic blood level or increasing their blood levels were asked to examine their stools regularly day after day It was found that such patients frequently returned and showed us the exact number of pills which they had ingested but which they had found in their stools apparently almost wholly unabsorbed The pills when removed from the stool were slightly decreased in size and their outer protective coating was missing However it was obvious that a great amount of the drug by this method of administration was not absorbed in these particular patients

It appears wiser in such cases therefore to change to a liquid solution of the thiocyanate recognizing however that accuracy of dosage would tend to be less by teaspoonful measurement than by pill To overcome this inaccuracy of teaspoonful doses which may vary from 4 c c to 6 c c in size it is best to give the patient a simple small test tube upon which one has scratched a level indicating exactly 4 c c If the potassium thiocyanate is made up in elixir of wild cherry in a proportion of 0 2 gm (gr 3) to each 4 c c each 4 c c may be substituted for one pill in the above described doasge

Toxic Symptoms of Thiocyanates — The use of the thiocyanates over a 10-year period in large numbers of patients has not resulted in marked toxicity in any case where the above rules were followed One of the earliest symptoms associated with the use of thiocvanate is fatigue It is difficult to say whether fatigue is a toxic symptom When patients reach a blood level around 6 to 8 mgm they often will say that they have noticed they are tired This tiredness is not severe If the use of the drug is continued and the blood level does not rise further this fatigue disappears or at least the patient becomes accustomed to it and no longer complains of it However if the blood level rises to 8 to 10 to 12 mgm this fatigue is definitely greater in most patients Even then however a very large percentage of the patients do not mind this fatigue even with such blood levels Blood levels from 10 mgm upward are however more apt to be associated with unpleasant effects Such effects must however be compared with the effects that occur if one gives large doses of any of the sedatives Such large doses of

drug should not be used in persons with congestive heart failure, with impairment of renal function, with easily provoked, recurring attacks of angina pectoris or with marked debility. The drug also should not be given to patients who are known to be uncooperative. The average cooperative patient, who is up and about actively, who may or may not have severe headaches, who is free of significant shortness of breath, angina pectoris, edema or renal nocturia, is the proper subject for trial of this therapy.

The dosage of thiocyanate cannot be given categorically for any one patient. It would seem from personal experience that it should be related to the body weight so that persons of heavier body weight, having more tissue and more intercellular fluid, will require a larger dosage in order to obtain a desired blood thiocyanate level. It therefore becomes necessary to experiment in each individual patient with the dosage and to use the blood thiocyanate level as the criterion for increasing or decreasing dosage. For some time the author has used the following plan of dosage and has obtained satisfactory results. He has prescribed potassium thiocyanate in the form of the enseal (Lilly) which comes in 0.065 and 0.2 gm. size (gr. 1 and 3). Generally an initial dose of 0.2 gm. 3 times a day for 3 days, followed by 0.2 gm. 2 times a day for 4 days, is a good way to start the drug. At the end of the first week a venous sample of blood is obtained at any time during the day and the blood thiocyanate level is determined by a competent technician. The chemical determination of the thiocyanate blood level is as simple as the determination of the blood nonprotein nitrogen. If the blood level is 6 mgm. or less, it is safe to continue 0.2 gm. twice a day for the second week. At the end of the second week the blood level is again determined and if it is not above 8 mgm., it is proper to continue the same dose for the third week. If at the end of the second week the blood level is above 8 mgm. but not above 10 mgm., it is best to cut down the dose slightly during the third week, prescribing one pill one day and two pills the next day and alternating in that fashion. If the blood level at the end of the second week is above 10 mgm., it is wise to decrease the dose to only 1 pill (0.2 gm. a day) or even omit the drug for 3 to 4 days. In this manner by weekly determinations for 4 or 5 weeks it is easy to calculate the daily dose needed to keep the blood level fairly constant. After that it is possible to continue the drug indefinitely, making blood determinations every 3 to 4 weeks. In general it is best to keep the blood level to somewhere around 8 to 10 mgm. Levels between 10 and 12 mgm. are permissible if blood levels are taken every two weeks and if such a level does not produce undue fatigue. In each patient it soon becomes easy to determine how much thiocyanate is necessary to maintain desired blood levels without blood determinations more than once in 3 or 4 weeks.

I have noted, as others have reported, that in some patients the blood level will remain, for example, around 6 or 7 mgm., despite increasing doses. In other

and the blood pressure returns to its former level In chart 5 are presented the effects of thiocyanate on the blood pressure level of a patient

The thiocyanates may be used constantly for many years in the same patient I have used them constantly for 6 years in several patients in whom at no time have there been any toxic manifestations and in whom fairly constant blood levels have been maintained with occasional variations in the dosage It should

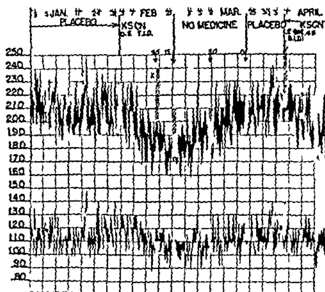


CHART 5 Home and clinic blood pressure curves of a patient with essential hypertension before during and after treatment with potassium thiocyanate The black wavy curves are the daily home readings the upper black curve the systolic and the lower black curve the diastolic The vertical broad hatched columns are the clinic readings The numbers just above each arrow are the blood concentrations of thiocyanates in mgm per 100 c c

be noted that patients may maintain a blood level for example of 7 to 9 mgm month in and month out and then suddenly without apparent change in dosage have rises or drops in blood level The reason for such sudden changes is not known It may be related to a change in the absorbability of the tablets used It should be noted also that the mode of action of thiocyanates in hypertension is totally unknown Test tube experiment indicates that the drug decreases the oxygen metabolism of growing tissue It tends to increase the blood sedimentation rate Beyond this nothing further is known The drug acts in some patients

sedatives might well be considered toxic, and certainly, if the sedative is pushed markedly the patient may be in a drowsy almost comatose state. In the case of thiocyanate the toxic symptoms that follow fatigue are variable. In the levels of 10 to 12 mgm., and occasionally 8 to 10 mgm., patients may have some nausea, occasional diarrhea and occasional vomiting, weakness is complained of occasionally in more intense manner so that the patient does not feel like doing much of anything. When blood levels are much above 12 mgm., the patient still may feel perfectly well but in a large number the symptom of weakness becomes more intense. There is then apt to be palpitation on slight effort, nausea is more evident and the patient may really feel ill. Progressively rising blood levels will result in a feeling of faintness and eventual collapse, and still higher levels may result in the development of psychosis. Skin manifestations may appear with long continued use and with blood levels around 12 mgm. They consist of varying types of eruption usually a maculopapular itching eruption which may be limited to various parts of the body such as the neck, upper chest, arms or legs; in very rare cases exfoliative dermatitis may occur. These eruptions disappear on omitting the drug and often do not recur when the drug is given again.

It is therefore necessary to tell patients that a feeling of lassitude may be expected and is a helpful reaction. This feeling of lassitude permits the high strung patient to relax and acts much like a sedative. Patients should be advised however that if they notice greatly increasing fatigue or weakness they should stop the drug for a few days; if the fatigue has not then disappeared they should omit the drug until they are next seen by the doctor. Persistent severe fatigue, the development of nausea, vomiting, abdominal cramps and diarrhea are indications for decreasing dosage markedly, but again such symptoms usually are associated with elevated undesirable blood levels. Finally, the use of the drug in renal disease, failure to follow blood levels or overdosage by unintelligent patients may result in such toxic symptoms as psychosis, delirium and collapse. If such severe toxicity should occur treatment is supportive with attempts to rid the body of the drug by clyses of saline. Rare instances of chronic "cabbage goiter" with myxedema are seen when high blood levels are maintained for a long period of time. In such cases the myxedema and goiter readily disappear without thyroid medication when the drug is omitted.

With due consideration for its toxic symptoms potassium thiocyanate may be used just as safely as other toxic drugs like digitalis and morphine. It has a definite place in the therapy of essential hypertension. Often it will relieve the major symptoms of severe headache as long as a proper blood level is maintained. Often it will lower the blood pressure moderately but not regularly so long as the blood level is maintained at 8 to 10 mgm. In many cases of mild degree a normal blood pressure level may be maintained with the drug. The drug is excreted completely in 2 to 3 weeks so that after its discontinuance symptoms reappear,

patients concerns the brevity of the preoperative observations which are used to compare with the postoperative results In the case for example of Smithwick s preoperative studies the data usually is obtained during a or 3-day period of observation[69] A curve of blood pressure and pressor reactions obtained during this period is compared later with results of the same tests postoperatively Unfortunately as already emphasized such a comparison does not supply a correct idea of the effect of operation unless the operation produces an absolute drop to a constantly normal blood pressure from an extremely high preoperative level Unfortunately such a result is not common and usual The reason that a 2 or 3-day period or for that matter a or 3 week period of observation before operation is inadequate has partly been discussed previously Not only is it inadequate because it is an extremely momentary period in the entire preoperative life cycle of the hypertensive patient under observation but because it is also an extremely tense and unusual period in that patient s life He knows at this particular time that he has a serious disease that requires a formidable set of operations which will be followed by a minimum period of 2 to 3 months up to 6 or more months of convalescent disability He knows also that there is no promise *of successful results in any given case He therefore cannot go through the period* of the 2 or 3-day preoperative observation in a nonchalant uninterested relaxed mood More correctly he is in a most intensely disturbed state at such times so that his blood pressure readings must be commonly at an abnormally elevated level Such tests are done partly in the physician s office and partly during hospital admission for a 2 to 3-day period This state of excitement cannot be removed by the locale of the test The result therefore is that the blood pressure levels obtained from the reactions of the blood pressure to a cold or breath holding test or to sedative tests are abnormally high It would follow therefore also that if such a patient were then merely subjected to simple skin incisions for the treatment of his blood pressure his postoperative levels would unquestionably be lower also The differences between such preoperative and postoperative levels could be considerable even without specific operation Differences of 40 or 50 mm Hg systolic and 10 or 20 mm diastolic could be obtained undoubtedly in many of these cases However in the perhaps 10 per cent of cases who drop completely to normal after operation and who before operation had a marked hypertension such control study is less important Unfortunately 90 per cent or so of the average cases sympathectomized do not fall into this category and must have adequate preoperative control study in order to know whether the operation has had some or no effect The best way in which such preoperative studies could be carried out properly would be if they were done always by the patient s physician himself rather than the surgeon or his team and even more important that they should be done in the family physician s office before discussing or mentioning the strong likelihood or desirability of operation to the

like a sedative, while in many patients it has absolutely no sedative effect so that in most people who have insomnia, it is necessary also to give a hypnotic before bed

SYMPATHECTOMY There is no longer any doubt that the operation of sympathectomy has a definite place in the treatment of essential hypertension The history of the development of sympathectomy as a therapeutic measure for hypertension apparently first began in 1923 when it was suggested by Danielopolu[7] The first operation seems to have been done by Adson in 1925 and reported by Rowntree and Adson[76] He removed the second, third and fourth lumbar ganglia without significant effect in a patient with malignant hypertension In 1927 Pieri[77] described his technique of splanchnicectomy for hypertension but did not describe his results

These initial efforts have undergone much elaboration and modification The first change was by Adson who cut the sympathetic nerves by resection of the anterior roots[78] This operation requiring laminectomy was apparently effective but has been given up because of its difficulty and high mortality In 1934 Craig after clinical studies by Brown carried out unilateral and later bilateral infradiaphragmatic splanchnicectomy, adding in a few cases the resection of the first and second lumbar ganglia[79] In 1935 Peet reported his initial studies of supradiaphragmatic bilateral splanchnicectomy[80] In 1937 Allen and Adson described subdiaphragmatic splanchnicectomy with lumbar ganglionectomy, adding in some cases partial adrenalectomy[81] In 1938 Smithwick Goldshine and the author had a patient subjected to a seven stage almost total bilateral sympathectomy without significant effect on the level of blood pressure In 1940 Smithwick[8] combining the Pieri Peet and Allen Adson methods described his two-stage bilateral transdiaphragmatic operation, by which he removes the entire great splanchnic nerves with their aortic branches and the sympathetic ganglia ninth tenth eleventh twelfth thoracic and the first lumbar and occasionally also the second and third lumbar ganglia and 6 7 8 and 9 thoracic Finally Grimson has reported a group of almost total bilaterally sympathectomized cases[83] The actual results in many of the above studies are widely divergent In a recent summary of 437 cases of essential hypertension followed 5 to 12 years after sympathectomy Peet[84] stated that ' rarely does surgical treatment result in a cure of hypertensive disease but it has given remarkable benefit and prolonged the life of many hypertensive patients'

Like most therapeutic studies of hypertension the studies of surgical therapy above noted are seriously marred by unintentionally unscientific methods of control The proper methods of controlled study for evaluating therapeutic results have been described already in previous sections of this chapter There are, however, some additional factors which also have not been controlled by the studies mentioned above The outstanding error in the preoperative study of these

patient Then such tests combined with the other adequate observations already mentioned would give a reasonable preoperative control level of blood pressure and blood pressure reaction It is therefore with tongue in cheek that it is necessary to view the reported results of sympathectomy except in those striking cases that have dropped dramatically from extremely high levels to perfectly normal ones or in those cases adequately followed and so reported adequately

Chart 6 shows the blood pressure levels in a patient before and after lumbothoracic sympathectomy This patient has now been followed for 7¾ years and the blood pressure levels have remained definitely and markedly improved This patient had known hypertension for 8 years prior to operation She had been followed 3 months prior to operation by means of weekly visits to the hypertension clinic during which 20 minute rest periods were carried out and the blood pressure determined during them and also by 4½ months of home blood pressure readings This period of preoperative study showed that the average clinic blood pressure level study was 2 0 systolic and 126 diastolic and the average home blood pressure was 204 systolic and 112 diastolic Following the bilateral thoracodorsal sympathectomy the average blood pressure level in the clinic during 20 minute rest periods and for a 7¾ year period has been 158 systolic and 100 mm diastolic The home levels during this entire period however have been 124 systolic and 80 diastolic This clearly shows that there has been definite improvement in the blood pressure level amounting to 62 mm systolic and 26 mm diastolic when using clinic levels only However the home levels indicate that the improvement has been much more marked so that the patient has a normal blood pressure with the readings taken at home during this entire 7¾ year period It is clear therefore that if we did not know what the home readings were in this patient we would not recognize the added benefit provided by sympathectomy The difference between the home and clinic levels in this and other patients represents the pressor response of the doctor s presence or of the environment of the office or hospital This pressor response masks many successful therapeutic results in hypertension

In Chart 7 are shown more striking results in a younger hypertensive patient This young man of 31 had known of hypertension only for about 6 months prior to seeing me He was seen from January 1943 until May 1943 and the upper line in the chart preoperatively discloses the average office levels In addition for 4 months he took his home blood pressure readings and these seem to average slightly lower than the office readings but not strikingly so This young man had constant albuminuria Intense headache was the presenting complaint In addition he had had an occasional burning sensation over the anterior chest of brief duration without relation to exertion Following bilateral lumbothoracic sympathectomy he had a dramatic drop to an absolute normal level of blood

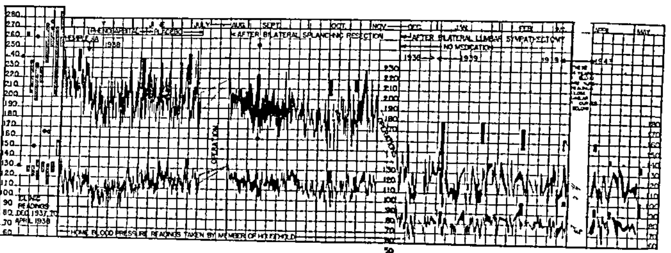


Chart 6 This chart shows 5½ years of preoperative and postoperative blood pressure observations The jagged continuous lines represent the home levels of blood pressure The vertical columns hatched or solid indicate the clinic blood pressure readings over a 20-minute rest period In July 1938 after bilateral splanchnic resection (Peet) there was no blood pressure improvement In November 1938 after bilateral lumbar sympathectomy markd drop in blood pressure resulted The end of the chart shows blood pressure in the last 2 months of 1943 The period between 1939 and 1943 is omitted for the sake of space but the levels were unchanged From 1943 to 1946 the blood pressure levels have persisted unchanged

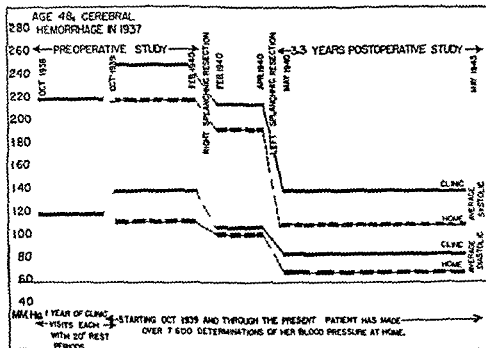


Chart 8 This shows the preoperative and postoperative average levels of blood pressure The clinic levels are indicated by solid black lines and the home levels by the broken black lines A period of 7 weeks at home elapsed between the first and second stages of operations The operation performed was the transdiaphragmatic lumbothoracic sympathectomy

He suffered from intense headaches every 1 or 2 weeks There was a marked family history of hypertension He was followed for 3 years more and both home and office readings were recorded He was subjected to sympathectomy of the lumbothoracic type and Chart 9 indicates that there was absolutely no effect upon the blood pressure level The reason for this failure is unknown

Personal observations of the effect of sympathectomy indicate that when successful the drop in blood pressure is extremely prompt i e within the first few weeks after operation However if there is considerable pain as a result of the discomfort around the operative scars the patient cannot relax and his blood pressure level may be somewhat elevated due to the pain stimuli However most pain is gone usually within 3 or 4 weeks postoperatively It is however stated that in some cases the blood pressure may drop during the course of 6 months to 1 year due to progressive relaxation of vessels However no carefully followed

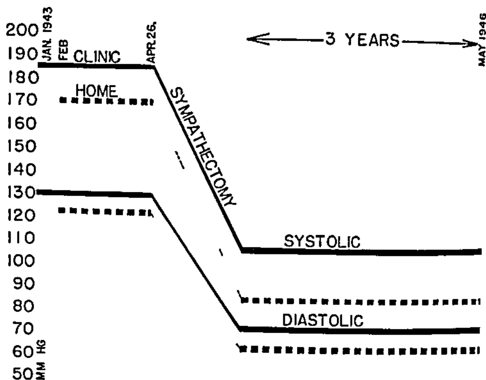


CHART 7 Blood pressure levels before and after lumbothoracic sympathectomy in a man of 31 with constant albuminuria and intense headache The heavy continuous black line represents office readings The dotted lines represent home levels

pressure both in the office and in the home This has persisted during these 3 years The albuminuria has cleared up completely and he has felt perfectly free of symptoms He has worked regularly in the past 2½ years It should be noted however that the home readings even here tend to be slightly lower than the office readings

Finally in Chart 8 are shown results of sympathectomy in a woman who already had had a hemiplegia prior to sympathectomy In this individual it is noted that there was a striking drop in both clinic and home readings following operation However after a period of 4½ years of normal home readings (not all plotted) and marked improvement in clinic readings there has been a gradual marked rise in both of these levels without apparent cause However preoperative severe headaches as yet have not returned

That age is not the only factor in the question of response, nor is the type of blood pressure level an absolute guarantee of response is disclosed in Chart 9 This young man of 23 was seen in 1940 when he had had hypertension for 5 years

As noted by Allen and Adson[66] and by Smithwick[67] extensive sympathetic denervation is associated with a marked drop in blood pressure and a tachycardia when the patient stands These postural effects are the usual findings in any successful case It is often so marked that the blood pressure will drop to undeterminable levels and the patient will faint unless provision is made to overcome it Such provision consists in the use of tight leg and thigh binders and a pressure abdominal belt These have to be worn for at least 2 or 3 months after operation The postural effect upon blood pressure will decrease gradually in the course of 2 or 3 months so that the binders may be removed gradually However observations of the author indicate that there is a mild persisting postural effect in many cases even as long as 3 or 4 years after operation In some cases this persisting postural effect is evidenced only by a tachycardia even when there is a satisfactory compensation in the blood pressure level itself It is of significance however that in patients whose home readings while seated have been frequently as low as 76 systolic and 50 mm diastolic there has been no faintness or significant tachycardia even 7 years after operation

There is no further doubt also that sympathectomy will result in many cases in a complete change of the electrocardiogram from evidences of left ventricular hypertrophy and left ventricular strain to normal tracings[69 66] The amazing thing about such change is the rapidity with which it may occur In Chart 4 such a change occurred within 3 weeks after operation The electrocardiographic changes after sympathectomy give us a very good idea of the true electrocardiographic picture of left ventricular strain and hypertrophy and indicate that obviously they are reversible It is also not rare to note that the heart may return from a slightly or moderately abnormal size to a normal size within a few weeks or months However it should be noted that in the case of the heart a decrease in size may result purely from the effect of postural hypotension with resultant inadequate filling of the heart due to venous pooling As I have personally demonstrated it may in some cases be worth determining the heart size in the recumbent position before and after sympathectomy to attempt to rule out this factor

The ocular fundi following sympathectomy also change despite the fact that the upper part of the body has not been sympathectomized Such change is therefore partly due at least to the general decrease in blood pressure level In many cases marked arteriolar spasm disappears and the arterioles gradually assume normal size However I have not noted any disappearance of marked arteriovenous nicking Cases with blurring or edema of the optic discs malignant hypertension may show postoperatively complete clearing of such marked changes

Adequate pre and post-operative studies of renal function have not been presented in detail in these sympathectomized cases so that the expected improve

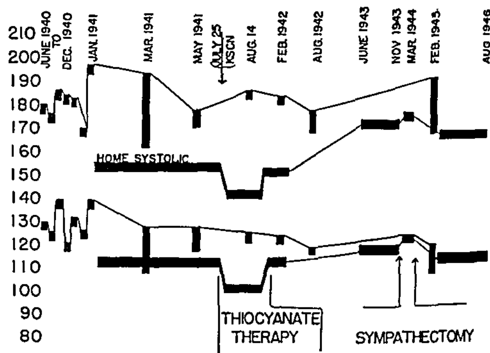


CHART 9 Blood pressure observations before and after lumbothoracic sympathectomy in a young man of 23 Electrocardiogram and heart size normal The black vertical squares and columns represent office blood pressure levels usually during 20 minutes of rest The horizontal black band represents home blood pressure levels The upper curves represent systolic and the lower 2 curves represent diastolic variations Thiocyanate therapy from July 25 1941 to November 16 1941 with blood levels between 6 and 9 mgm Unilateral lumbothoracic sympathectomy November 1943 was followed by pneumonia Operation on second side postponed until March 1944

case of such nature has been presented and I feel that such effects probably are more apparent than real and are due again to inadequate observations

There are some postoperative complications associated with radical sympathectomy one of which is the result of slight nicking of the pleura and resultant pneumothorax In such cases the positive pressure intratracheal anesthesia regularly used during operation prevents a collapse of the lung and such pleural nicks are easily repaired Another sequel of the operation when a bilateral removal of the second and third thoracic ganglia in men is performed, is inability to empty the seminal vesicles so that sterility will result This is not due to impotence since the normal sex act usually can be carried out If the second and third ganglia are not removed bilaterally, then there is risk of an unsuccessful result Pain due to neuritis often results due to the resection of the twelfth ribs and injury to intercostal nerves

patients into three groups according to the pattern or type of blood pressure The most successful operative results were obtained in those people who had a relatively narrow pulse pressure The poorest results were obtained in those who had an extremely wide pulse pressure His type #1 patients are those whose basal resting pulse pressure is less than one half the diastolic pressure for example 180/130 His type #2 patients are those in which the pulse pressure ranges between one half of the diastolic blood pressure and one half the diastolic pressure plus 19 His type #3 are those whose pulse pressures are above the type 2 group i e 250/110 A second criterion of good results is sex the female sex showing definitely better results than the male sex in any of these three types A third criterion is the effect of the sedative test preoperatively The sedative test consists of giving a large dose of sedatives and observing the drop in blood pressure One regime consists of giving 0 2 gm (gr 3) of sodium amytal at hourly intervals for a total of 3 doses The blood pressure is recorded before during and after the drug is given It is recorded at 15 minute intervals until 1 hour after the last dose and then taken hourly throughout a 4 hour period The patient is kept in bed in a quiet room or screened so that there are no outside stimuli A note is made as to whether the patient is asleep during each blood pressure reading since the purpose is to have the patient completely asleep at some time during the test Failure of the blood pressure to drop markedly near or close to normal puts the patient in an unfavorable group However as is evident this is merely group consideration and does not tell clearly what is going to happen to any specific patient s blood pressure after operation Likewise since successful response in those patients with wide pulse pressure is reported to be between 50 per cent and 80 per cent depending on sex then one is forced to conclude that there is a 50 to 80 per cent possibility of some response in that group Similarly personal experience with the sedative test has shown that a patient in whom there is no drop with sodium amytal may secure a markedly successful effect upon blood pressure level by sympathectomy and vice versa A patient of mine who had a sedative drop in blood pressure to 98 /0 had no response to even an almost total sympathectomy It is necessary to reiterate however that Smithwick s present criteria for selection are based upon retrospect analysis of preoperative and postoperative blood pressure findings These blood pressure findings as well as all reports on surgery for hypertension are however open to the criticism of inadequate control study already discussed in detail so that the criteria for selection likewise cannot be accurate

Cognizance should also be taken of the recent use of caudal anesthesia as a preoperative test in a small group of cases[47] It was found that the drop in blood pressure produced by the test correlated very well with the postoperative results This however is also an experimental criterion at this time Previous comparisons of preoperative spinal anesthesia on blood pressure levels with the

ment has not been clearly proven However, release of vasoconstriction of blood vessels supplying glomeruli should be expected to improve renal function Some cases with mild albuminuria and red blood cells in their urine have shown postoperatively complete clearing of these abnormalities

Symptomatic improvement occurs in many cases The chief symptom relieved is severe headache This has been reported, and I can substantiate its occurrence even when there was no apparent improvement in blood pressure In such cases the possible psychotherapeutic effect of operation must be considered but also the fact that in many cases there is actual improvement, which might be demonstrated in the home readings but which is not visible in the office or clinic due to the masking pressor effect of the latter

My personal studies with pressor tests before and after operation have not given me any clear help in determining whether or not the operation will be successful Smithwick however, after reviewing his cases found that a marked pressor response places the patient in a more favorable group for operation Following operation there may or may not be a decrease in the range of pressor response, the range meaning the amount of rise in blood pressure produced by the test Some successful cases however, may have a postoperative decrease in range even to normal range The top level to which the blood pressure rises after the pressor test is called the ceiling, this is lower in benefited cases but the success of operation is seen easily in the top clinic or office readings themselves without pressor tests On the other hand the pressor test ceiling after operation, and occasionally preoperatively may be much less than the actual height at which the blood pressure is frequently found in the clinic or office without pressor test stimulation For example, a patient who after operation reacted to the cold and breath holding tests by a hypo-reactor , normal range showed marked and greater reactivity of blood pressure in the clinic At one visit he might have a top blood pressure of 196/104 and at another clinic visit a top reading of 130/80 The top readings at the clinic were much higher than the ceiling obtained by the pressor tests It is clear therefore that the pressor tests do not necessarily indicate the degree to which the blood pressure in some of these patients fluctuates In other words the range of blood pressure after pressor stimuli may be much less in such cases than the range produced by other environmental stimuli

Choice of Patients for Sympathectomy —The past 7 or 8 years have been proving periods for the effectiveness of sympathectomy in some patients with hypertension and in looking backward certain criteria have evolved for the selection of patients[69, 84] First, the best evidence thus far has been presented by Smithwick who after sympathectomizing 156 patients analyzed his results to see if there were any means of picking out the reasons why some patients had successful results and others had no response According to his data he was able to divide

resemble those seen in many young early hypertensive patients who are apt to be dismissed with a diagnosis of emotional hypertension

The promising results in some hypertensive patients makes one ask whether the operation increases the life expectancy in the successful case The various reports are strikingly conflicting and their conclusions must still remain uncertain Woods and Peet[89] on the one hand state that splanchnicectomy does increase life expectancy while Flaxman[90] on the other after comparing Woods and Peet s results with medically treated cases concludes that there is little difference in mortality between the two groups Recently Peet and Isberg[91] reported a 5 to 12 year follow up of 437 patients and again stated that operation prolonged life Personally I feel certain that those cases in whom there is a complete drop of blood pressure to normal and in whom such drops remain for a number of years must obtain a beneficial effect upon the vascular system and a prolongation of life The other cases in whom there is only a mild or moderate degree of drop in blood pressure are the ones in whom the greatest differences of opinion will result from statistical studies because as already pointed out so much of such apparent improvement is not due at all to operation but to incorrect preoperative control blood pressure levels

It has been asserted that the drop in blood pressure after sympathectomy is non specific and is one that occurs after any operation[91 9*] Such an explanation is reasonable when one remembers that great asthenia and inactivity after major operations do cause a lowering of the blood pressure Studies of hospital records for the effect of non specific operations on the blood pressure by Rojas[93] indicate that there is a small postoperative drop of about 10 or 15 mm Hg systolic due to such non specific effect If on the other hand this study had taken into account that sympathectomy really consists of two separate operations then scientifically they should have multiplied their non specific result by two This would give a possible drop of 30 mm Hg systolic as a non specific effect It would indicate also that improvement in blood pressure of 30 to 40 mm Hg systolic as a result of sympathectomy is open to question unless such drops are to absolutely normal levels The argument that a non specific effect of operation is the reason for the permanent drop in blood pressure is also ruled out by the obviously negative results attained in a number of patients already subjected to a unilateral sympathectomy and the patients discharged to go home and convalesce from some momentary complications before undergoing the second stage of the operation In such cases as in Charts 6 and 8 there is no evident effect upon the blood pressure following the first stage of sympathectomy As a matter of fact it is well known that a bilateral resection must be performed before there is any significant effect upon the blood pressure level Finally true non specific effect of operations upon the blood pressure is really only a momentary affair not lasting more than a month or two after operation

subsequent effect of sympathectomy showed no correlation[85] Perhaps a better correlation will be shown by studies now under way using small doses of anesthetic in spinal anesthesia with the belief that such small doses will act primarily on the vasomotor fibers

Regardless of how skeptically and critically I have viewed less well controlled studies of sympathectomy, my own data viewed just as critically have convinced me that no medical therapy has ever equalled the results of sympathectomy[86] Certainly the blood pressure can be lowered to marked degree by potassium thiocyanate in large doses with high blood levels and kept down for prolonged periods but constant attention must be given to such patients, and their activity becomes greatly depressed by the marked effects of the drug If the drug is used, however in mild hypertensive patients an excellent result can be obtained without depressing effects A patient can be ordered to bed and given very large doses of sedatives with a similarly good effect on the blood pressure This however is not a practical means of existence No one can point to a single well controlled case of severe essential hypertension in which medical treatment has brought the size of the enlarged heart the abnormal electrocardiogram and the elevated blood pressure back to normal In my experience sympathectomy has accomplished this in some cases with persistence of success for 8 years to the time of writing

The optimism and enthusiasm rising out of these findings must be tempered by some provoking facts and queries First the operation, no matter how extensive has completely abolished rises in blood pressure produced by excitement in only a small proportion of cases probably less than 10 per cent In most cases the home readings of the blood pressure show rises associated with arguments great physical or emotional strain markedly cold rooms, deaths in the family, etc However the average home existence of these patients does not often produce such rises and the pressure may be as low as for example 80/64 On coming to the clinic or office however the initial readings of such patients taken immediately after the patient enters the examining room are usually in the abnormal levels even if on resting they drop to or close to normal This variation between initial readings and readings at the end of a rest period also accounts for the differences of opinions in previous papers concerning the effect of sympathectomy or any therapy If one merely records or emphasizes the blood pressure at the end of rest in such postoperative patients as in the data of Smithwick this may give the erroneous impression that the blood pressure is 140/90 for example whereas if one always also takes the initial readings immediately after the patient enters the office one will frequently and usually find elevated readings, for example of 180/110 These common variations of blood pressure after sympathectomy indicate that large denervated areas are left and that the hypertensive tendency still exists The fluctuations in blood pressure in these patients

that medical treatment has been unable to halt the progress of these changes and that the disease is severe enough to produce such changes Such changes to which we refer are definite increase in the size of the heart development of moderate left axis deviation (in the absence of increase in weight) development of electrocardiographic evidence of left ventricular strain development of inconstant or constant albuminuria and finally development of definite changes in the ocular fundi The age factor is a matter not yet settled as time goes on one must seriously consider those people over 55 years of age who now because of age receive no serious consideration for sympathectomy

Given a patient who is seen for the first time with established hypertension namely a persistent variety that does not drop to normal but in whom there still is no evidence of cardiovascular renal damage then the same procedure applies with regard to observation as in the previous earlier group In such a group of patients with persistent although still markedly variable hypertension in whom there is no demonstrable cardiovascular disease one may readily advise the patient that the chances for living a goodly number of years *even without sympathectomy still is great in most of such patients* The development or finding of fresh hemorrhages in the fundi would seem to be good reason for advising sympathectomy but even then only after reasonably long observation of the blood pressure levels Even in those cases where one demonstrated definite cardiac enlargement definite evidence of left ventricular strain or definite hemorrhages *in the fundi it is quite proper to try a reasonable period of medical treatment* and observation Such observation also will permit the establishment of control levels of blood pressure in the ambulatory state with which to compare any future levels obtained if sympathectomy is carried out The presence of chronic unilateral renal disease is not a contraindication to sympathectomy In fact it seems that hypertensive patients with chronic bilateral pyelonephritis respond exceedingly well to sympathectomy[60] *Time may prove the same to be true for* bilateral renal disease such as chronic glomerulonephritis The degree of chronic vascular nephritis as judged by renal biopsies at time of sympathectomy also bears no relationship to the operative results Success occurred in those with marked arteriolar renal disease as well as in those with absent or minimal biopsy changes

Essential hypertension still is a medical disease which should be evaluated and studied primarily by the internist whose experience is obviously much greater than the surgeon s in the evaluation of cerebral cardiac and renal functions The postoperative evaluation should also be primarily in the hands of the internist The decision to operate in hypertension should rest on a bilateral opinion of an internist thoroughly cognizant of the details of the disease and of a competent surgeon There is however a third individual who must enter into the decision for sympathectomy and that is the patient In advising or suggesting

after which the patient recovers full vigor and activity When successful, the effects of sympathectomy, however, are of many years' duration

Mention has been made already of the fact that in sympathectomy as with any other form of therapy the home readings may be lowered or normal after the therapy, while the office and clinic readings remain unchanged or only slightly lower This will account for the reports in the literature that 1) there was a marked improvement of symptoms without drop in blood pressure, or) some of the signs, such as enlargement of the heart or abnormal electrocardiograms, reverted to or towards normal and yet the office blood pressure level remained unchanged after operation[94] In such cases I feel certain that the study of home readings would indicate the blood pressure actually had been markedly improved by sympathectomy, but the pressor effect of coming to the doctor s office resulted in masking this therapeutic drop However the therapeutic home drop was quite sufficient to remove the load from the heart for most of the 4 hours of the day and thus the heart size and electrocardiogram returned to or towards normal

Smithwick s criteria using pulse pressure particularly does not adequately help one to decide in any individual case If such criteria were followed strictly, then one would be forced to submit millions of young hypertensives to sympathectomy It must be agreed with Allen and Adson and with Smithwick however that patients in congestive heart failure, patients with marked impairment of renal function and obviously debilitated patients are poor candidates for any surgery and certainly should not be subjected to sympathectomy Unfortunately this has not been the attitude of many internists who refuse to offer sympathectomy to those patients who are at least good surgical risks but do offer the operation to almost moribund patients There is really no longer any basis for such an attitude Such a viewpoint can only mean that patients with hypertension operated upon successfully have not been observed by such physicians It also suggests that these physicians have not made it their business to study the subject adequately

Given a patient with hypertension it is my plan to consider his therapy in the following manner If he is a young hypertensive with variable blood pressure, which often drops to normal levels one invariably finds on physical or other examination no evidence of vascular damage This individual represents one of many millions of people He certainly should not be subjected to sympathectomy but rather to the previously described medical tratment Having established satisfactory normal office blood pressure levels by regular observation and having determined the normal size of the heart the normal appearance of the electrocardiogram and the normal concentrating ability of his kidneys these should be used as guides during the ensuing years The demonstration by these various yardsticks that the disease is producing damage in such an individual indicates

should be urged strongly to change her common attitude of extreme finicky cleanliness to one of commonsense moderation The constant washing of woodwork and windows and dusting under out of the way places that rarely need such constant attention should be clearly discouraged Most such women would be able therefore to have much more leisure time if their almost maniacal folly could be converted into a more sensible attitude The same over anxiety concerning the life of every relative and neighbor must be converted to a more moderate feeling The housewife also needs vacations and some means of arranging for them can always be more successfully made through other members of the family than through the patient since such women usually will remonstrate vehemently against leaving what they think is an indispensable position at home Vacations in the summer frequently involve sea bathing It would appear reasonable to advise the advanced hypertensive patient not to go into ocean water that is cold It is well known that merely inserting the hand up to the wrist in ice water causes an intense rise in blood pressure The same sort of reaction although to less degree occurs if one goes into cold water at 60° to 70 F The author has actually taken several hypertensive patients whose blood pressure levels were well controlled walked into the ocean with them and observed the effect upon the blood pressure while in the ocean By merely walking in and slightly splashing about such activity and entrance into the ocean water exerted definite pressor effects which are undesirable Where ocean water is warm such as in southern parts of the country or in really warm lake water there is probably no contraindication to such activity Exposure to sun is not objectionable providing the patient feels comfortable It is more likely that the heat would cause vasodilatation and some lowering of the blood pressure

It becomes self-evident that the hypertensive patient should not engage in competitive sports of any sort because he takes all activity much too seriously He usually has an intense desire to win so that the sport no longer is true relaxation or fun Activities of any sort that involve squeezing pushing or heavy lifting cause tremendous rises in the blood pressure of hypertensive patients and great rises of blood pressure even in the normal individual The simple act of great exertion at defecation will result in the normal individual often having a rise of 100 mm Hg systolic in blood pressure because squeezing involves a closure of the epiglottis and a great rise in intrathoracic and intraabdominal pressure in other words it is the Valsalva experiment

Walking at a normal moderate pace is a good form of physical activity for the average hypertensive patient Contrary to recent studies of the effect on the blood pressure of hypertensive patients[95] the author has found that walking at an average rate does not cause a rise in blood pressure All previous studies of the effect of such physical activity upon the blood pressure have been studied only at the very end of the physical activity The author has carried out studies

surgery to such patients, it is necessary to indicate clearly the uncertainty of success, which is still a purely statistical matter That he, a male for example, may be one of 62 per cent, who might have a good response in type no 1 or one of the 38 per cent who do not should be clearly told to him It should be realized also that such statistical data for a male in type no 1 is based solely on Smithwick s report of 34 male type no 1 patients The experimental nature of the treatment should be explained also to him, so that he will know that there is a possibility of recurrence of his hypertension The problem of sterility in the male, if adequate denervation is carried out, must also be properly explained and seriously considered in the young unmarried or the childless married male in such cases only a severe form of the disease is an adequate reason for operation before marriage The operation should not be performed merely for the relief of symptoms Symptoms almost always can be relieved by medical means Finally the operation should be performed only by surgeons who are properly trained in this field and if it is carried out by such trained men then the mortality rate can be kept below 3 per cent In a disease that has usually existed for some years there is only rarely an excuse for brief preoperative studies or emergency decisions An emergency sympathectomy indicates that the subject is a poor risk and in such surgery should not have been seriously considered

Other Forms of Treatment The psychic side of patients with essential hypertension should be treated This applies as much to patients who are free of symptoms as to those with symptoms Analysis of their general activities their anxieties and their fears will permit the physician to point out more sensible attitudes In view of the hypertensive patient's highstrung personality as already discussed he is particularly prone to perturbed, emotional states and one should make an effort really to rearrange his life where necessary It will be found that many such people carry on an 18 hour a-day business activity and as a result have no play nor true mental relaxation It becomes, therefore, essential in such cases to insist upon an 8- or 9 hour day of work and the remainder of the day for following an entirely different and placid line of activity The development of a non competitive hobby such as writing reading painting, wood working etc is definitely helpful Such people should allow adequate time for meals so that the common 16 minute lunch period should be changed to a full hour for both eating and relaxing afterwards A period of relaxing before dinner should be the rule Frequent vacation periods should be encouraged whether they be merely weekends or weeklong periods Such vacations should again not consist of visiting a nearby metropolis and carrying on an 18 hour day of entertainment and activity The asymptomless hypertensive patient as well as those with symptoms should have a minimum of 8 hours unbroken sleep, and the use of sedatives should be encouraged whenever the patient feels unable to fall asleep within a half hour period after retiring The hypertensive housewife

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in which the blood pressure was followed at 3 minute intervals throughout the actual period of walking one half to one mile In such instances it was found that the majority of people do not have any significant rise in the systolic blood pressure but rather have a significant drop in the diastolic blood pressure This widened pulse pressure is the normal response to physical activity One would feel therefore that this vasodilatation actually may be of some value Following cessation of walking the diastolic and systolic blood pressure promptly returned to the level existent before the start of the walk Walking and other mild exercise such as non competitive golf are, however, to be guided carefully with proper attention to the state of cardiac function The old dictum of Mackenzie that the cardiac may do anything he wishes that does not produce discomfort remains unchallenged

Ineffectual Forms of Treatment There are at this time no other proven worthwhile specific forms of treatment that will really lower the blood pressure in essential hypertension Various medications have been used but have no value watermelon extract, mistletoe garlic extracts, aminophylline, theobromine etc are all without any effect upon the blood pressure level if one uses control methods of observations already described Potassium iodide has no known effect upon the blood pressure level Nitrates are of only momentary evanescent value Recently mannitol hexanitrate with the trade name of nitranitol has been given wide medical publicity and yet this also has little or no effect upon the blood pressure level Careful studies with this drug by the home blood pressure method have shown that there may be improvement in blood pressure of 5 to 10 mm in systolic readings but such change is obviously insignificant even when judged by our more careful technique of study

Recently Grollman and his co-workers have reported six cases in which sodium chloride restriction of marked degree was used with apparent good effect upon blood pressure in essential hypertension[96] However analysis of this brief initial report indicates that here also an adequate form of blood pressure control was not used A period of 2 to 3 weeks of bed rest without therapy was followed by the low salt diet Actually there is no evidence that after 2 or 3 weeks the blood pressure would not drop farther Furthermore the use of sodium chloride capsules unknown to the patient as salt should be given as a control in such a study together with the exact replica of the diet Finally examination of the figures of blood pressure drop in this paper indicates an extremely slight effect which may be non specific Grollman states that the low sodium diet has been effective in lowering the blood pressure of hypertensive animals He also feels that the failure of all past sodium chloride restriction diets has been due to the fact that restriction has been inadequate Repetition of this work using controls described in this chapter should easily answer the question whether such a diet has any significant effect upon the blood pressure I have recently studied 6 patients on

this diet and have seen no significant effect on the level of the blood pressure

Recently the use of synthetic vitamin K synkavite has been reported to be effective in lowering the blood pressure in daily doses of 5 mgm orally[97] This study like many others was reported in a manner to indicate clearly that adequate control of blood pressure levels was not carried out and the results are therefore open to great doubt I have personally used the same drug in doses from 25 mgm up to 500 mgm daily for periods of 6 to 8 weeks without the slightest evidence of hypotensive effect in essential hypertension

In the past few years the rice diet has made its debut[98] This diet consists of a very low protein high carbohydrate (rice) diet taken month in and month out The original papers on this diet certainly did not meet the scientific criteria already outlined for the evaluation of therapy in hypertension However a recent paper by Kempner[99] requires even more attention since he stated that in a large number of hypertensive patients he observed a decrease in the size of their hypertrophied hearts and a return of the inverted T waves of the electrocardiogram to erect normal T waves I am now in the process of studying the effects of this diet

Another form of diet therapy which has often been reported as successful *in hypertension is weight reduction Obesity occurs extremely frequently in patients* with essential hypertension Many writers on the subject of hypertension state that weight reduction often has a lowering effect upon the blood pressure Review of all these studies indicates that in none of them was there an adequate control of blood pressure level before instituting the diet Proper control would require that the patient be seen regularly and frequently immediately prior to giving the diet Usually however in the office or clinic the obese hypertensive patient is examined and immediately placed upon a weight reduction diet and the blood pressure seems to drop markedly Such drops however are due as already pointed out to the normal progressive drop in blood pressure resulting from frequent repetition of visits to the office following the initial visit I have studied 40 obese hypertensive patients in a most careful manner and have found that weight reduction of 20 to 40 pounds has absolutely no effect upon the blood pressure level *On the other hand extreme weight reduction to the point of malnutrition* and emaciation will lower the blood pressure in the same manner that any *malnutrition emaciation or state of debility will act Such a degree of* therapy obviously is not sensible or practical for hypertension Weight reduction however in essential hypertension is desirable in the obese subject because it certainly does improve the ability to carry on normal activity without shortness of breath It also obviously decreases the work of the heart It should therefore be carried out in the obese hypertensive patient with such an object in view The attainment of a normal body weight should be the goal although rate of

weight reduction need be only moderate It is to be noted also that there are many hypertensive patients who are lean and thin, showing clearly that obesity is not the cause of essential hypertension, but rather that obesity is part of the broad physical build of the average hypertensive patient

There is no reason for restricting the protein intake of patients with essential hypertension There is a widespread belief among people that the so-called red meats are more harmful than the other forms of protein, but there is no scientific evidence for such belief The patient should be allowed to eat any form of meat he wishes In the absence of elevated levels of nonprotein nitrogen there is no occasion for restricting the protein intake in any way There is no evidence that restriction of cholesterol intake in any way modifies the course of essential hypertension despite the feeling by some investigators that foods containing cholesterol predispose to sclerosis of blood vessels There is no reason for restricting fluid intake in the uncomplicated case of essential hypertension If, however there is evidence of cardiac failure with congestive signs and edema formation a normal fluid intake can be maintained, if the patient is placed on a low salt intake the low sodium preventing the formation of edema, regardless of fluid intake In the case of patients with essential hypertension, who already have damage of renal function it becomes essential that their fluid intake be even greater than normal in order to permit an adequate clearing of the blood of the end products of protein metabolism by means of a polyuria

Alcoholic drinks in moderation have no harmful effect upon uncomplicated essential hypertension Several ounces intake of alcohol produces a generalized vasodilatation and a general state of relaxation It is therefore, a helpful agent The average hypertensive patient does everything rapidly, including eating the habit of sipping a cocktail before dinner prevents the patient from immediately sitting down and wolfing his dinner The use of more than several cocktails however is unwise since it often results in a state of physical overactivity and an undesirable state of cerebral stimulation and overeating The author however, must say that he has seen patients with moderately severe hypertension who during or shortly after a state of alcoholism have shown markedly lower levels of blood pressure than in their non inebriated state The author does not however recommend this as a form of therapy for lowering the blood pressure

The use of tobacco in moderation has no known chronic deleterious effect in essential hypertension Until such time, therefore, as tobacco is shown to have such an effect one cannot honestly advise patients to give up smoking Hypertensive patients carry out all of their activities with great vigor and often to excess It is for that reason that they tend to be excessive smokers Where there is obvious excess and the author feels that more than one package of cigarettes a day is clearly too much, patients should be advised to reduce their consumption The presence of peripheral arteriosclerosis with intermittent claudi

cation or the presence of angina pectoris would also be reasons for reducing markedly the use of cigarettes or other forms of tobacco There are occasionally patients in whom it can be demonstrated that smoking a cigarette may elevate the blood pressure However unless one is willing to study each patient carefully with this in mind one cannot advise a patient to give up smoking completely with any assurance or scientific basis The use of beverages containing caffeine such as coffee and the various cola drinks is permissible in moderation in hypertensive patients Excessive use will cause cerebral stimulation and is undesirable The same holds true for the use of tea Complete restriction of tea or coffee is not indicated

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CHAPTER XV

THE FUNCTION, FORMATION, DESTRUCTION AND PATHOLOGICAL PHYSIOLOGY OF THE BLOOD CELLS

By Cyrus C. Sturgis

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Introduction and Normal Standards

In order to have a clear conception of the various diseases affecting the blood and blood forming organs it is necessary to have a thorough knowledge of the normal histology and physiology of the blood cells their mode of formation and destruction and their pathological physiology As a basis for further discussion it may be said that the adult male of average height and body weight namely 5 feet 9 inches in height and weighing 172 pounds will have the following normal findings pertaining to his blood and vascular system

1 A total blood volume of about 5 300 c c

2 A red blood cell count of approximately 5 0 million per cubic millimeter

3 A total cell mass in the circulation of 2 390 c c which contains in the neighborhood of 933 grams of hemoglobin

4 The above amount of hemoglobin contains 3 125 grams of iron (approximately 80 per cent of the entire body content) and is capable of combining with

1 80 c c of oxygen an amount calculated to serve an individual for approximately 5 or 6 minutes when at complete rest and for only a fraction of a minute during strenuous exercise

5 The mean corpuscular volume of the erythrocyte averages 88 cubic microns the mean corpuscular hemoglobin 29 o micromicrograms and the mean corpuscular hemoglobin concentration 32 92 per cent

6 The mean diameter of the red blood cell is 7 2 microns and the mean thickness varies from 1 65 to 2 microns

Structure of the Erythrocytes

As far as our present knowledge is concerned the sole function of the erythrocyte is associated with its hemoglobin content which in turn has to do principally with the transportation of oxygen from the lungs to the tissues and to a much lesser extent as a carrier of carbon dioxide

All evidence indicates that the erythrocyte is admirably constructed to perform its principal duty It is accepted that the normal red blood cell has a biconcave shape and may be looked upon as a bag with some degree of elasticity and flexibility a bag which contains a stroma or framework This acts as a support for the semisolid jelly like hemoglobin which is in a colloid state Although it is not possible to demonstrate that the erythrocyte has a cell membrane on microscopic examination it is assumed that one does exist and that it is semipermeable in nature permitting the passage of water and certain dissolved substances such as glucose and sodium chloride but not of colloids This membrane is thought to be exceedingly thin perhaps only the thickness of a few molecules It is considered to be made up of layers of protein and lipoid substances

The mature erythrocyte in man does not contain a nucleus nor can it be demonstrated that it consumes oxygen or glucose in metabolic processes Hence it does not possess some of the essential criteria of the living cell There is every reason to look upon the circulating mature erythrocyte as a lifeless object containing a substance hemoglobin which has the remarkable capacity to take up and give off oxygen under circumstances which are ideal for the purpose of transporting that essential substance from the lungs to the tissues According to the observations of Hartridge[1] the biconcave shape of the erythrocyte is the most efficient one which can be assumed for the sake of its primary function This configuration permits the entire cell contents to become saturated in the same interval of time which would not be possible in a sphere In the opinion of Hartridge the shape of the erythrocyte permits (1) the maximum surface for the bulk of the cell (2) a change in volume to occur without straining the envelope unduly (3) the complete saturation of all parts of the contents of the cell with oxygen simultaneously Thus due to unknown forces nature has provided the

most efficient shape for the erythrocyte to perform its vital function, the suspension of which would result in the death of a person within a few minutes

Hemoglobin

The red coloring matter of the blood, the *hemoglobin* performs the essential function of transporting approximately 99 per cent of all the oxygen from the lungs to the tissues To accomplish this the venous blood enters the lung capillaries with the hemoglobin 70 to 75 per cent saturated with oxygen and leaves with an oxygen saturation of about 95 per cent In addition to the transportation of oxygen the hemoglobin also is accountable for at least two other functions which are subordinate in importance to the former They are the transportation to the lungs of between 2 to 10 per cent of all carbon dioxide formed in the tissues and its action as one of the important buffer substances of the blood

Hemoglobin itself is a conjugate protein which is equipped uniquely to accomplish its purpose It consists of two parts namely, a protein of the histone class called *globin*, which makes up 96 per cent of the molecule and an *iron containing pigment* portion *heme*, making up 4 per cent The latter is composed of four pyrrol nuclei which are joined together in a distinctive fashion to form a compound called protoporphyrin [$C_{32}H_{32}N_4(COOH)_2$] The porphyrins in nature are known to unite with various metals and form pigmented substances For instance, the combination of this substance with copper forms the coloring matter of the shell of certain birds and the union with magnesium is the basis for the color of chlorophyll of plants When iron combines with protoporphyrin a substance which has been designated as ' heme' is formed This compound then unites with globin to form hemoglobin the respiratory blood pigment of vertebrates The chemical constitution of hemoglobin, therefore may be represented as the combination of protoporphyrin plus iron plus globin

Recent studies indicate that the molecular weight of hemoglobin is 68,000 basing the calculation on the belief that the hemoglobin molecule contains 4 molecules of iron As blood of human male adults contains an average of 15 6 to 12 9 grams of hemoglobin per 100 c c of blood and the iron content of hemoglobin is 0 335 per cent each 100 c c of blood would contain 52 to 43 milligrams of iron combined with hemoglobin

The Combination of Hemoglobin with Oxygen

Although hemoglobin has other functions as previously mentioned, by far the most important is the transportation of oxygen The ability of hemoglobin to combine or release oxygen almost instantly under certain circumstances is dependent on the presence of iron in the molecule It is recognized that the two

elements unite in accordance with the law of definite proportions and hence two atoms of oxygen join with one of iron It is important to keep in mind from the standpoint of the anemias that the ability of the blood to transport oxygen is directly proportional to the amount of hemoglobin which it contains With each gram of hemoglobin 1 34 c c of oxygen will unite and if 100 c c of blood contains 15 6 grams of hemoglobin then this quantity of blood is capable of carrying 21 c c of oxygen As the arterial blood usually is only 95 per cent saturated however this amount would be approximately 20 c c If the average male adult has a blood volume of 5 400 c c then the entire amount of oxygen present in the blood stream at any given moment would be 1 080 c c This would supply the body with an adequate quantity of oxygen for only 4 or 5 minutes when at complete rest and for only a small fraction of this time during a period of strenuous exertion

A small amount of oxygen is carried also in solution in the plasma but this liquid combines with 60 times less oxygen then does hemoglobin and hence is of no great importance in supplying the respiratory gas to the tissues It has been calculated by Barcroft that if there was no hemoglobin in the body and hence the tissues were dependent solely on the amount of oxygen carried in solution in the plasma then it would be necessary to have a total circulating fluid medium in the vascular system of 350 liters

It has been pointed out by Barcroft[2] that the properties of hemoglobin make it the ideal respiratory pigment Furthermore he emphasizes that by enclosing hemoglobin in the erythrocyte nature has spared the circulating blood a greatly increased viscosity and of even greater importance as the pigment is inside the cell it is prevented from exercising its considerable osmotic pressure effects and thereby upsetting significantly the fluid balance of the body

It should be pointed out in connection with the anemias that when the hemoglobin content of the circulating blood falls below a certain level characteristic symptoms such as dyspnea palpitation ease of fatigue and weakness will appear The intensity of these is usually in direct proportion to the level of the circulating hemoglobin and they first become apparent when the hemoglobin level falls to 70 per cent or less although this varies somewhat in different persons It is not difficult to understand the mechanism of the production of such symptoms namely that they are dependent on anoxemia and an effort of the blood to increase the suboptimal supply of oxygen This subject will be discussed in more detail elsewhere but the purpose in referring to it now is to emphasize that the body attempts to compensate immediately for an inadequate blood supply to the tissues by two main mechanisms namely to remove more oxygen from the arterial blood than the normal amount which averages about 25 per cent and to increase the circulatory rate which accounts for the palpitation and tachycardia especially on exertion which is observed constantly in patients with anemia

Metabolism of Hemoglobin and Production of the Bile Pigments

Both the bile pigments, bilirubin and biliverdin, are responsible for the color of bile although the former predominates It is well established that these pigments are derived from the hemoglobin, which is liberated from the effete red blood cells by a process of hydrolysis This transformation is accomplished by the cells of the reticuloendothelial system, which are present principally in the liver, Kupffer's cells the bone marrow and the spleen The polygonal cells of the liver play no role in the formation of the bilirubin but merely excrete it from the blood stream into the bile

It is estimated[3] that approximately 25 grams of hemoglobin are liberated daily as a result of normal red blood cell destruction Of this about 15 to 20 grams are utilized in the formation of new erythrocytes, and 5 to 9 grams are transformed into bilirubin According to the authors previously cited the liver excretes from 200 to 370 milligrams of bilirubin daily in the bile which represents about 4 per cent by weight of the hemoglobin from which it is derived It is estimated that one gram of hemoglobin yields about 40 milligrams of bilirubin

The bilirubin is formed by (1) hydrolysis of hemoglobin to heme and globin, (2) the opening of the tetra pyrrol ring of heme and (3) the elimination of iron In the passage of the blood through the liver two actions occur, namely, first, the bilirubin is removed from the blood stream by the hepatic polygonal cells and, second the bilirubin is transformed from a colloidal state, perhaps bound to protein, bound bilirubin , to a crystalloid one Free or crystalloid bilirubin, as contrasted with colloidal bilirubin is excreted readily in the bile and in the urine In obstructive jaundice, as the bilirubin has passed through the hepatic polygonal cells and hence is in the crystalloid form, it is excreted readily through the kidneys and also gives the direct reaction On the other hand, when excessive amounts of bilirubin are present in the circulating blood, and it has not passed through the hepatic cells, then the bilirubin still is in the colloidal or bound state Hence it is not excreted through the kidneys and requires the addition of alcohol to the serum reagent mixture to effect the reaction which indicates that it is the indirect type

In summary then it may be said that the bilirubin of normal serum resulting from hydrolysis of hemoglobin gives only the indirect reaction It is then said to be in the colloidal state and is perhaps bound to protein On the other hand the bilirubin of bile having passed through the polygonal cells gives both the direct and indirect reactions which indicates that some change has occurred in its passage through these cells and that the bilirubin is now in the crystalloid state

When free or crystalloid bilirubin reaches the upper intestine the normal bacterial flora reduce it to urobilin which is brown in color Two closely allied substances are formed from urobilin namely, stercobilin, which is the normal

brown pigment of the intestines possibly identical with urobilin and second by further chemical reductions the colorless urobilinogen is formed This is absorbed by the portal system of blood vessels and carried to the liver where it is reconverted to bilirubin and excreted for the most part in the bile A small amount however is eliminated by the kidneys The latter step in the normal excretion of urobilinogen forms the basis of the well known urobilinogen test for liver function Its rationale is as follows if the function of the liver is so impaired that it cannot reconvert the circulating urobilinogen to bilirubin and excrete it in the bile then an excessive amount will be carried to the kidneys and lost in the urine Hence an excessive amount of urobilinogen in the urine is considered as indirect evidence that the liver has suffered significant damage

Bilirubin Content of Blood Serum

The amount of bilirubin in the blood serum may be determined by means of the qualitative van den Bergh test or by the simpler icterus index estimation In my experience the normal serum bilirubin concentration in adults varies from 0 1 to 0 8 milligrams per 100 c c of serum While it is true that a large percentage of normal persons have serum bilirubin concentrations of less than 0 5 milligrams per 100 c c nevertheless clinical experience has shown that it is advisable to consider the normal upper level to be 0 8 milligrams per 100 c c

The icterus index is determined by comparison of the color of the serum or plasma with a normal standard solution of 1 10 000 potassium bichromate The color of this standard is 1 0 Normal serum gives a reading of from 4 to 6 and persons with intense jaundice from 40 to 50

It is not my purpose to discuss in detail the formation and excretion of bilirubin except to mention that the amount of bilirubin in the blood serum and the amount of products derived from it afford an idea as to the rate of blood destruction Hence this information is of value in estimating the role played by this process in the production of any given anemia It should be kept in mind that an elevated blood bilirubin *does not necessarily indicate an increased rate of blood destruction* as other causes may be operative in this connection In the presence of an elevated blood bilirubin the following possible causes should be considered (1) an increased destruction of erythrocytes (2) an impairment of the functional ability of the reticuloendothelial system (3) injury to the polygonal hepatic cells with a diminished ability to excrete bilirubin from the blood into the bile (4) the possibility that the bile ducts may be obstructed

Index of Hemolytic Destruction

According to Miller Singer and Dameshek[4] the output of urobilinogen in the urine and feces is a reliable index of blood destruction As the total amount of

urobilinogen in the urine does not exceed 1 to 2 milligrams daily, it is essentially correct for this purpose to determine the amount of this substance in the feces. Since the sole source of the latter is the hemoglobin of the red blood cells this may be employed as an index of erythrocyte destruction in the body. In order to do this however, it is necessary to compare it to the total mass of circulating hemoglobin in the blood which may be calculated from the concentration of hemoglobin per 100 c c of blood and the total blood volume. Such an index is derived from the following equation

$$\text{Hemolytic Index} = \frac{\text{Average of 4 days daily output of fecal urobilinogen (mgm)} \times 1{,}000}{\text{Hemoglobin (gm per 100 c c)} \times \dfrac{\text{total blood volume}}{100}}$$

This index gives the total amount of urobilinogen excreted in the stools daily which is derived from 100 grams of hemoglobin. The result thus obtained the normal hemolytic index" as they designate it varies between 11 1 and 20 8 milligrams which indicates the amount normally converted from 100 grams of hemoglobin. These investigators observed that a decreased amount was found in patients with polycythemia hypochromic anemia and in the post splenectomy state. In such conditions the decrease varied from 20 to 69 per cent. An increase was observed in a number of conditions as follows pernicious anemia from 204 to 1,131 per cent congenital and acquired hemolytic anemia from 287 to 1,672 per cent Cooley's anemia from 700 to 2,159 per cent, and in one case of Gaucher's disease the increase was 61 per cent

An index such as this is not practical to apply in clinical medicine but it serves a useful purpose in demonstrating that increased blood destruction does occur as a contributing or the main mechanism in the production of certain anemias

Formation of the Red Blood Cells

One of the most controversial questions in hematology deals with the origin and early development of the cells of the circulating blood. For many years there have been two schools which hold opposing views. One group the monophyletic school contends that all mature red and white blood cells have a common ancestor which in general has been described as a primitive, basophilic mononuclear cell of mesenchymal origin. On the other hand, those who support the view of the polyphyletic school, maintain that there are two or more separate primitive sources for the blood cells. The statements just recorded summarize the main difference in thought between the two factions but there are a number of subdivisions of each main group to which attention cannot be given here. In general, it does not appear justifiable or necessary to draw a definitive conclusion

between these two schools of thought at this time as far as clinical hematology is concerned

For the purposes of understanding the various types of blood disorders it appears satisfactory to adhere to the idea that the earliest recognizable precursor of the erythrocyte which is in marrow preparations is the primitive erythroblast This cell measures about 12 to 14 microns in diameter the cytoplasma is scanty and deeply basophilic the nucleus fills a relatively large portion of the cell the chromatin pattern is reticular and one or more rather sharply outlined nucleoli are present Cells of this type are capable of mitotic division in the bone marrow and of differentiating into megaloblasts

The next cell which develops in the maturation of the red blood cells of the adult is the megaloblast This cell is prominent in the bone marrow of patients with pernicious anemia and allied macrocytic anemias during relapse By some it is thought not to occur in normal bone marrow but it is my belief that such cells may be present in the normal marrow of an adult in small numbers They are observed constantly in normal fetal bone marrow but in adult life when present in large numbers such a state represents a maturation arrest or a reversion to the embryonic type of blood formation These cells are large sometimes measuring 20 microns or more in diameter The nuclei are characterized by a finely granular chromatin the nucleoli have indistinct outlines and are present in numbers of two to five the cytoplasm is basophilic and in the most primitive cell of this type shows no evidence of containing hemoglobin Cells with mitotic figures at this stage may be observed in abnormal bone marrow

The normoblast is the next stage in the development of the red blood cells There are three characteristics of this type of cell which differentiate it from the megaloblast The first is that the size of both the cell and the nucleus is less second the chromatin of the nucleus tends to become more compact and densely staining third the cytoplasm becomes less basophilic and obviously contains hemoglobin Cells of this class may be divided into the early and late normoblasts depending upon the degree to which the three characteristics just named have developed

The final stage in the erythrocyte before it becomes mature and emerges into the blood stream is the reticulocyte This cell contains no nucleus as it is lost either by dissolution or extrusion The characteristic finding in such a cell which permits its identification is the presence of a network or reticulum of varying extent either confined to a small area or extending throughout the cell which stains light blue with a vital stain such as brilliant cresyl blue With Wright s stain the reticulum is dissolved and then appears as a diffuse bluish tint spread evenly throughout the cell The reticulocyte is somewhat larger than the average mature erythrocyte measuring about 9 1 microns in diameter as opposed to 7 5 microns for the former There are fairly large numbers of reticulocytes in the

normal adult bone marrow, but only 1 per cent or less are present in the circulating blood

Clinical Significance of Changes in Rate of Maturation of Erythrocytes

Only brief mention need be made here of the changes observed in the development of the erythrocyte in the various anemias, as this subject will be discussed under the heading of each type of blood diseases As a general statement it may be said that in pernicious anemia and allied macrocytic anemias the bone marrow is characterized by a maturation arrest at the megaloblast stage, and hence sternal puncture in a patient with one of these types of anemia will disclose many megaloblasts In patients with an iron deficient anemia, however the striking change is arrest of maturation at the normoblast stage When the erythrocyte is arrested at the megaloblast stage, it is known that in many if not all, instances this is due to a deficiency of the erythrocyte maturing factor which is elaborated in the stomach as a result of the interaction of the extrinsic and intrinsic factor of Castle and which is stored in the liver In the patient, in whom the arrested maturation is at the normoblast stage, it is due in many instances to the deficiency of iron

Sites of Erythrocyte Formation

In almost all mammals, blood formation is limited at first almost entirely to the liver, but after the initial half of embryonic life this function is taken over largely by the spleen The red bone marrow appears in the second or third month of fetal life in humans, and henceforth this tissue gradually assumes the function of blood production entirely It is recognized that blood formation in the liver and spleen is almost entirely nonexistent at birth In early childhood the marrow of almost all of the bones is red and active in the production of blood cells Gradually the process becomes limited to the vertebrae, ribs sternum bones of the skull, the os innominatum and to some extent in the proximal epiphyses of the femur and humerus Normally blood formation ceases in the shafts of the long bones beginning in the fifth to the seventh year and it disappears entirely by the eighteenth year When this occurs the red marrow in the active bones is replaced by fat It should be noted that in case of need however, as results for example in the development of a severe anemia the fat which is normally present in bone, often is replaced rapidly by active hematopoietic tissue According to Custer and Ahlfeldt[5] the change from a fatty to a totally cellular marrow may occur in pigeons, under experimental conditions in the amazingly brief interval of two days Although the long bones show some response by the development of a

cellular marrow, when the need furnishes the stimulus it is the ribs sternum and vertebrae in which the activity is the greatest

Extramedullary Hematopoiesis

It is known that when severe anemias are present especially in infants and young children erythrocytes may be formed again in other sites than those which are normally active at any given age This is looked upon as a compensatory mechanism just as the change from a fatty to a cellular marrow occurs in some of the long bones under the same circumstances The extramedullary formation of blood may be active in many sites in the body but it is observed most frequently in the spleen the liver and lymph nodes More rarely it may be present in the adrenals adipose tissue and other unusual locations Such abnormal formation of blood is observed in erythroblastic anemia pernicious anemia in the various types of leukemia in osteosclerosis, chronic hemolytic anemia and various other severe and prolonged anemic states[6, 7]

It is of interest to note that, when extramedullary hematopoiesis is active it is likely for unknown reasons to be associated with the appearance of immature red and white cells in the circulating blood It suggests that whatever is the regulatory mechanism which acts to prevent the entrance of immature cells into the circulating blood under normal conditions it fails when the blood is formed elsewhere than at its normal sites

Length of Life of the Erythrocyte

There is lack of agreement concerning the duration of life of the mature red blood cell by those who have made a study of the question It is most commonly stated that it remains in the circulation about 30 days but some contend that it is somewhere between 15 and 120 days In humans some of the most acceptable studies to determine this have been done by transfusing the red blood cells of one group into the recipient of another group and then by agglutination reactions ascertaining how long the transfused cells survive By this method Ashby[8] concluded that the span of life of the erythrocyte was between 30 and 100 days with an average of 83 days Employing the same technic Dekkers[9] found that the period of survival of the erythrocytes was between 54 and 74½ days Although this method undoubtedly gives valuable information it cannot be considered as entirely accurate The two criticisms advanced have been that in the blood which is given to the recipient there are erythrocytes of all ages Second it cannot be considered that the recipient of a blood transfusion is an entirely healthy person and hence the length of life of the red blood cell is not observed under normal conditions

Of considerable interest in this connection are the observations of Hawkins and Whipple[10] who estimated the length of life of the erythrocyte in dogs by the collection of bilirubin through a bile fistula in experimental animals. They base their conclusions on the knowledge that for each gram of hemoglobin destroyed in the circulation there are 40 milligrams of bilirubin liberated. Following the establishment of a bile fistula they either destroyed by phenylhydrazine or removed by bleeding many of the erythrocytes. In this way the animal was forced to fill his circulation with many new erythrocytes. At this time the bile pigment fell to low values, because the cells were added recently to the circulation and hence were not being destroyed. Eventually the erythrocytes, large numbers of which had been added to the circulation at approximately the same time underwent disintegration. It is at this time that there will be a notable increase in the bile pigment excretion through the bile fistula. By this method the authors have estimated that the length of life of the erythrocyte in such an animal averages about 124 days.

This figure is in accord with the growing belief that the life of the erythrocyte is longer than had been supposed previously. As Wintrobe[11] points out, the longevity of the red blood cell has been calculated to be as brief as 14 days in man and even of shorter duration in animals. If these statements were true then from 50 to 350 c c of blood approximately 22 to 150 c c of packed red blood cells would be destroyed daily in a normal adult under conditions of moderate or limited activity. In his opinion probably the smaller figure is correct.

In general it seems logical to assume that the length of life of the erythrocyte in the normal adult under the average conditions of life is approximately 100 days. On this basis therefore one would assume that one one hundredth of the total number of red blood cells in the body are destroyed each day. The figure of 25 trillion is given by Haden[12] as the total number of erythrocytes in the body and if this is true, then one one hundredth of this number (25 billion) would be destroyed daily.

Method of Red Blood Cell Destruction

It seems strange that the normal process of erythrocyte destruction, which proceeds so actively each day in fairly large proportions in the body, is so little understood. In the comprehensive review by Rous in 1922[13], after considering all possible known cause for red blood cell destruction, he concludes that it comes about for the most part by fragmentation. It is the opinion of Rous that the trauma to the erythrocytes, as they were buffeted about in the circulation, causes them to disintegrate finally to a fine dust which was removed from the circulation by the spleen. When one considers that the mature erythrocyte in the circulation is a lifeless cell an inanimate object which performs its functions passively and

has no process of repair it is to be expected that it would wear out if subjected to sufficient mechanical injury This theory although probably correct is possibly incomplete and difficult to prove For the present however it is the most plausible one available It is also assumed that the effete and damaged erythrocytes and portions of erythrocytes in the circulation are engulfed and destroyed by the cells of the reticuloendothelial system which widely distributed in the body are present in the largest numbers in the spleen the liver and the bone marrow

Methods of Estimating Volume and Hemoglobin Content of the Erythrocyte

It is possible to calculate the mean corpuscular volume the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration by utilizing the red blood cell count in cubic millimeters the amount of hemoglobin in grams per 100 c c and the volume of packed cells (hematocrit reading) in cubic centimeters per 100 c c of blood Hence by these simple determinations valuable and accurate information may be obtained which is of great use in clinical hematology

Calculation of the mean corpuscular volume —

$$\text{Mean Corpuscular Volume (M C V)} = \frac{\text{Volume packed red cells c c per 1 000 c c}}{\text{Red blood cell count millions per cubic mm}}$$

The results obtained by the use of the above formula are expressed in cubic microns Example Red blood cell count 3 0 volume of packed cells 34 5 per 100 c c of blood The mean corpuscular volume would be 345 divided by 3 0 or 115 cubic microns

If it is assumed for the sake of convenience that the average mean corpuscular volume is 88 cubic microns then the Volume Index which is an expression of the mean corpuscular volume in terms of an arbitrary normal can be calculated as follows

$$\text{Volume Index} = \frac{\dfrac{\text{Packed cell volume per 1 000 c c}}{\text{Red blood cell count in millions per cubic mm}}}{88}$$

The normal mean corpuscular volume usually is given as varying between 86 and 96 cubic microns with an assumed average of 88 cubic microns In macrocytic anemia as in pernicious anemia the cell volume usually averages from 110 to 120 in untreated cases but I have seen it as high as 140 cubic microns In general it can be said that as the red blood cell count approaches normal in the

macrocytic anemias the more nearly the volume of the cells becomes normal. The volume index commonly is regarded as varying normally from 0.90 to 1.10.

Determination of the mean corpuscular hemoglobin concentration. — This calculation, when considered with the mean corpuscular volume, provides the most useful information of all the various ratios concerning the red blood cells. The mean corpuscular hemoglobin concentration expresses the ratio between the packed red blood cells and the amount of hemoglobin in grams and, therefore *measures the concentration of the hemoglobin in the red blood cells as if it were in solution.*

$$\text{Mean Corpuscular Hemoglobin Concentration (M.C.H.C.)} = \frac{\text{Hb. gm. per 100 c.c.} \times 100}{\text{Vol. packed red cells c.c. per 100 c.c. of blood}}$$

The result of the above calculation is expressed in per cent. Example: If the hemoglobin in grams per 100 c.c. of blood is 8.5, the volume of packed cells per 100 c.c. is 28 c.c. Then the M.C.H.C. is $\frac{8.5}{28} \times 100 = 30.3\%$.

If it is considered arbitrarily that the normal concentration is 33 per cent, then the M.C.H.C. may be expressed in terms of normal by a simple proportion or the calculations may be simplified by multiplying the M.C.H.C. by 3. This will then express the results in the terms of the *Saturation Index* (S.I.). For example, the above M.C.H.C. in terms of the saturation index would be 30.3 × 3 or 0.903.

Another index which is available but one which in my experience adds very little to an understanding of the changes in the anemias and therefore of little use in clinical hematology, is the mean corpuscular hemoglobin. This value is obtained by the following calculation:

$$\text{Mean Corpuscular Hemoglobin (M.C.H.)} = \frac{\text{Hemoglobin gm. per 100 c.c.}}{\text{Red blood cell count, millions per c.mm.}}$$

Example: A hemoglobin of 7.8 grams per 100 c.c. of blood and a red blood cell count of 2.5 millions per cubic millimeters would give an M.C.H. of 7.8 divided by 2.5 or 31 micromicrograms. The average M.C.H. usually is considered a varying from 27 to 31 micromicrograms. A distinction should be clearly recognized between the M.C.H.C. and M.C.H. as they represent different values. The former (M.C.H.C.) expresses the concentration of hemoglobin in the erythrocytes in terms of percentage whereas the latter (M.C.H.) indicates the average amount of hemoglobin by weight contained in a red blood cell indicated in terms of micromicrograms. In my experience the M.C.H.C. has been a much more useful calculation and it is not often that the information from the M.C.H. is utilized.

The color index still is regarded as helpful especially by the older group of hematologists who utilized this ratio as the only one available before the indices were introduced into clinical medicine It does serve a useful prupose despite the mild indifference with which it is held by many of the present day hematologists It is of course especially valuable when a hematocrit is not available which is often the case with many practitioners and hence by no means should it be entirely discarded The *Color Index* is calculated by dividing the hemoglobin in per cent by the red blood cell count in per cent of normal The difference of opinion arises as to what one should regard as a normal red blood cell count and hemoglobin It has been our custom at the University of Michigan to consider the normal red blood cell count as 5 0 per cubic millimeter and the hemoglobin as 15 6 grams per 100 c c as representing 100 per cent Hence

$$\text{Color Index} = \frac{\text{Hemoglobin in grams} \times 6\ 4}{\text{R B C count in c mm} \times 20}$$

For example if the hemoglobin is 50 per cent or 7 8 grams per 100 c c and the red blood cell count is 2 5 millions per cubic millimeter the

$$\text{Color Index} \frac{7\ 8 \times 6.4}{2\ 5 \times 20} = \frac{49\ 9}{50\ 0} = 1\ 0$$

The color index is therefore easily calculated from simple laboratory information which usually is readily available Furthermore when the technic is done properly the information is reliable If it does nothing more than indicate clearly that the macrocytic anemias with a high color index such as the pernicious anemia type and hence the ones that are commonly amenable to liver therapy differ from the iron deficiency variety with a low color index which are benefited by iron therapy the determination of such a ratio is well worth while

Cell Thickness — On the assumption that the red blood cell is a short cylinder it is possible to calculate the average corpuscular thickness by the following formula

$$T = \frac{CV}{\pi \frac{(D)}{(2)}}$$

where T is the corpuscular thickness CV the mean corpuscular volume and D the cell diameter The normal thickness of the erythrocyte is given by Haden[12] as 2 microns whereas Wintrobe[14] gives it as 1 65 microns According to Haden the average thickness of the red blood cells in various pathological conditions is as follows obstructive jaundice 1 60 microns pernicious anemia 2 2 microns simple microcytic anemia 1 6 microns chronic hemolytic anemia 3 02 microns

Rarely is the average thickness calculated in clinical hematology This is

because there is not often a need for this type of information, and in addition because it is of greatest usefulness only in the diagnosis of the various types of hemolytic anemias. Furthermore, it is usually possible to recognize spherocytes in the fresh blood preparations or in stained films. In many instances these cells have a small diameter and hence are very properly designated as microspherocytes. In such a condition it would be possible to have cells with an increased mean corpuscular volume, and yet the average cell diameter might be less than normal. This change can be explained only on the basis that the erythrocytes had assumed the shape of spheres instead of the normal biconcave form.

DIFFERENCES IN SIZE AND SHAPE OF ERYTHROCYTES
MEAN DIAMETER AND ANISOCYTOSIS

As one views a well prepared blood film through the microscope, the erythrocytes have an almost identical appearance. Each one is round or slightly oval and contains the same amount of hemoglobin; they are approximately the same size, although there may be some slight variation in diameter. It has been observed[15, 16] that in healthy adults the average diameter is 7.2 microns with a normal variation from 6.69 to 7.72 microns. Usually it is considered that the normal extremes of size are 6 microns and 9 microns. That is, any cell with a diameter of less than 6 microns is designated as a microcyte and one with a diameter greater than 9 microns a macrocyte. While it is true that by measuring the diameter of 200 cells and then determining the average diameter information of value in clinical medicine is obtained, it is a procedure which is little employed today. This is because it is too laborious and also because it gives less reliable information than the estimation of the cell volume which is a far more simple process.

According to Haden[12] the mean diameter is a much less sensitive indicator of change in cell size than is the cell volume as indicated by the fact that a 14 per cent increase in diameter is associated with a 46 per cent increase in cell volume. In general it can be said that variations in cell diameter have the same significance as the changes in cell volume. For example, it is to be expected that the average cell diameter in patients with pernicious anemia will be increased and in iron deficiency anemia it will be decreased.

Price Jones Curve

Beginning in 1910 and continuing with a series of publications until 1929 Price Jones reported on the average normal diameters of the erythrocytes and the changes associated with the various types of anemias. He advocated the measurements of 100 cells and the tabulation of these findings in the form of a chart as shown in Fig. 1.[17, 18] This type of information gives data which are not furnished

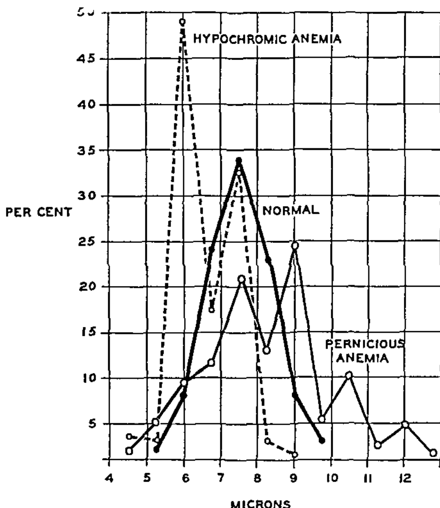


Fig 1 The curve (Price Jones Curve) shown by the heavy dark lines indicates the incidence of the erythrocytes that have various diameters in normal circulating blood It will be observed that a small percentage of cells measure only slightly over 5 microns and about an equal number are as large as 9 75 microns The great majority of cells however are 7 5 microns in diameter The same type of measurements from a patient with a microcytic hypochromic anemia due to chronic hemorrhage is shown by the curve with the dotted lines Some of these cells are as small as 4 5 microns in diameter and a few as large as 9 microns but the great majority are 6 microns in diameter In such a curve the peak is said to be to the left of normal In a patient with pernicious anemia and a red blood cell count which is below 2 0 million per cubic millimeter some cells are as small as 4 5 microns and a few as large as 12 75 microns The largest number measure 9 microns in diameter and the peak of the curve is to the right of normal A third characteristic of the Price Jones curve in the blood of patients with pernicious anemia is that the outline of the curve is not smooth as it is in normal blood but it has a jagged appearance

by the measurement of the cell volume In the first place it indicates the degree of anisocytosis as shown by the percentage of cells which are small and those which are large It also determines the diameter of the cells which are in the majority For example, in pernicious anemia usually the largest percentage of red corpuscles are those with a diameter of 9 5 microns whereas in iron deficiency anemia the greatest majority of cells have a diameter of 6 5 microns Although this information is useful, it is now utilized rarely, as studies by means of the cell volume based on the hematocrit and red blood cell count are more reliable, less difficult to obtain, and the changes in cell volume are more sensitive indicators than the cell diameter

The use of the halometer to determine the average cell size and the degree of anisocytosis[19] is helpful but rarely employed in most laboratories Its use is based on the theory that, when a beam of light is transmitted through a blood film, it is diffracted by the erythrocytes into spectral colors By this technique it is possible *to detect the mean diameter, the amount of anisocytosis and the degree of* poikilocytosis According to Wintrobe such a method is convenient for quickly finding the mean diameter and useful in following changes in average diameter of the same patient [0]

The precise significance of anisocytosis is difficult to state If such a change is undeniably present, then it is safe to conclude that the blood is not normal for only slight alterations in the size of the erythrocytes occur in health Such a change however, may be present in many types of anemia, and hence it cannot be considered as specific for any given variety It should be kept in mind that reticulocytes in general have a greater diameter than the average red blood cell, and hence when they are present in sufficient numbers, this may be a contributing factor to anisocytosis

Poikilocytosis

Normally the erythrocytes are round or only slightly oval and show almost no variation in shape The presence of unmistakable alterations in shape indicate always a pathological variation in the circulating blood For example all patients with pernicious anemia, when the red blood cell count is below 2 8 millions per cubic millimeter have definite changes in shape which become more pronounced as the anemia increases in severity When it is below 1 0 per cubic millimeter these alterations are among the most striking observed in hematology In certain anemias poikilocytosis is the outstanding feature of the changes in the blood For example in sickle cell anemia a large percentage of the cells have sickle shapes or other bizarre forms In ovalocytosis many of the cells assume an oval shape which gives the condition its name Changes in shape, which are distinctive such as in sickle cell anemia are diagnostic but poikilocytosis may occur also

in many other forms of anemia and as such is indicative only of anemia and not of any specific type

Another change in shape is that of spherocytosis occurring in hemolytic anemias This is discussed under the heading of cell thickness and also in the section dealing with the hemolytic anemias

SIGNIFICANCE OF CHANGES IN RETICULOCYTES

Estimation of the number of reticulocytes in the circulating blood is a valuable procedure in clinical medicine because it is the most reliable single index of the activity of the erythropoietic tissue Normally the circulating reticulocytes are present in numbers not exceeding 1 per cent One fact only is known with reference to a reticulocyte which is of clinical importance and this is that it is a young cell, just emerged from the bone marrow and the greater the amount of reticulum present the younger the cell When the bone marrow is stimulated to form new cells in greater numbers than normal, and the marrow is capable of responding then the numbers of reticulocytes increase in the circulating blood This may for example occur in patients who have extensive hemorrhage following which reticulocytes will often increase to 10 or 12 per cent This is especially true in chronic hemorrhage following the therapeutic administration of iron Of great importance is the response of the reticulocytes to potent therapy in patients with pernicious anemia in relapse In suchp atients the reticulocytes may increase usually on the fifth to the sixth day of treatment to 30 or 40 per cent This is discussed in more detail under the section of treatment in pernicious anemia

A reticulocytosis is valuable also from a diagnostic standpoint for it is an indication that, whatever may be the cause of the anemia it is not concerned primarily with the inability of the patient to produce erythrocytes For example, a reticulocyte percentage which commonly reaches 10 to 16 per cent is seen in the chronic hemolytic anemias in which the cause of the anemia is an increased destruction of red blood cell In one patient whom I observed with the acquired type of chronic hemolytic anemia, 95 per cent of all the cells were reticulocytes

SIGNIFICANCE OF OTHER IMMATURE ERYTHROCYTES IN CIRCULATING BLOOD

The presence of other immature forms of erythrocytes in the circulating blood such as normoblasts cells containing nuclear fragments or Howell Jolly bodies Cabot s rings and erythrocytes with diffuse basophilia are like the increased reticulocyte percentage, indicative of increased activity of the red blood cell forming tissue in the bone marrow As they are present in smaller numbers and

usually following a much greater stimulus to erythrocyte formation, estimation of their number does not give as satisfactory evidence concerning the degree of activity of the erythroblastic tissue as does the reticulocyte count It should be emphasized also that, when reticulocytes are stained with Wright's stain, the reticulum is dissolved and appears as a diffuse bluish gray tint in the red blood cells Hence cells which exhibit diffuse basophilia with Wright's stain, have the same significance as those with reticulum Cells containing punctate basophilia should be regarded as young erythrocytes, which usually in some way have been injured by a toxic agent Such cells are most frequently observed in lead poisoning

Criteria for Determining Specific Changes or Deficiencies in Red Blood Cells

It has been recognized by hematologists for many years that certain changes in the circulating blood are indicative of various types of activity which are of assistance in the classification of the different varieties of anemia[1] The changes tabulated below indicate certain significant alterations, which may be observed in the more important types of anemia

Active Cell Regeneration — Increase in the number of reticulocytes, basophilia, nucleated red blood cells Howell Jolly bodies, Cabot's rings, slight to moderate increase in the mean corpuscular volume, if reticulosis is marked increase in number of erythrocytes

Decreased Regeneration Due to Depression of Bone Marrow — Diminished number or absence of reticulocytes, no basophilia no nucleated red blood cells no change in cell measurements decrease in number of erythrocytes

Increased Hemolysis with Active Bone Marrow — Increase in bilirubin of the plasma exceeding the normal of 0 8 mgm per 100 c c persistent striking increase in the reticulocytes increase in the mean corpuscular volume due to the greater number of reticulocytes count variable, often spherocytes (cells with increased thickness) present

Deficiency in Antipernicious Anemia Factor — Increase in the mean corpuscular volume often exceeding that observed in any other type of anemia a normal mean corpuscular hemoglobin concentration (saturation index) a decrease in the number of erythrocytes in proportion to the decrease in the hemoglobin content of the blood in other words a high color index

Deficiency in Iron — Decrease in the mean corpuscular hemoglobin concentration or the amount of hemoglobin per cell, marked reduction of hemoglobin as compared to the reduction in the number of cells (low color index), a decrease in the mean corpuscular volume, if the iron deficiency is pronounced normal or diminished reticulocytes

The Leukocytes

Normal Number of White Blood Cells in Circulating Blood

It is generally accepted that the normal number of leukocytes in the circulating blood varies between 6 000 and 10 000 per cubic millimeter but these limits should not be accepted too rigidly In the first place in my experience leukocyte counts as low as 5 000 per cubic millimeter are encountered not infrequently in apparently healthy persons and also it is recognized that about 10 per cent of normal persons have a white blood cell count which is somewhat above 10 000 per cubic millimeter It is suggested therefore that the lower limit of normal be placed at 5 000 per cubic millimeter and that slight increases in the number of leukocytes be accepted as not necessarily indicating an abnormal condition especially if they are transient The latter changes usually are associated with the normal or physiological changes which are discussed below

Errors in Counting the Leukocytes

The two types of errors commonly encountered in determining the leukocyte count should be constantly kept in mind They are (1) those due to the inexpertness of the technician and (2) anticipated technical errors which are inherent in the method When the latter alone are taken into account these possible mistakes are considerable It is accepted that the major errors are in sampling[21] although they may result from improper mixing of the cells and diluting fluid and from inexpert filling of the counting chamber by capillarity It is estimated by Bryan Chastain and Garrey[1] that there is an average error of ± 241 cells ± 35 cells per cubic millimeter when 10 unit hemocytometer areas of one square millimeter each and a dilution of 1 to 20 are employed Wintrobe[22] points out that a mean error may amount to as much as 600 cells when the leukocyte count is 7 000 per cubic millimeter and an area of 4 square millimeters (one chamber) is counted or an error of 425 cells may be made if two chambers or 8 square millimeters are used By these calculations when the count is 16 000 per cubic millimeter the probable error would be 900 cells if the count is made in one chamber only Hence even in the hands of an expert technician if the actual count were 7 000 per cubic millimeter the error under the optimum circumstances for accuracy would allow a permissible range in the total leukocyte count from 6 400 to 7 600 per cubic millimeter and if the actual number were 16 000 per cubic millimeter it might be within the range of 15 000 to 16 700 per cubic millimeter The errors which are recognized as occurring in the differential count are discussed on another page

Physiological Variations in Leukocytes

It has been established that irregular and sometimes pronounced fluctuations occur in the total leukocyte count in normal persons These are of no great importance from the standpoint of the practicing physician except that in some instances they may be interpreted incorrectly as indicative of an important change in the leukocyte count with pathological implications It is now accepted generally that (1) these variations are frequently within the range of normal that is, between 5,000 and 10,000 per cubic millimeter, but they may be greater than normal (2) the fluctuations are usually associated with increases in the actual number of neutrophils but they may also affect the lymphocytes (3) the apparent increase in the number of white blood cells in the circulating blood usually is due to a redistribution of these cells in the body and does not indicate an actual new formation of white blood cells

Leukocyte Count at Various Times During the Day

It has been determined that the white blood cell count tends to be lowest in the morning under basal conditions at which time it ranges between 5 000 and 7 000 per cubic millimeter It has been observed by Kennon Shipp and Hetherington [3] in a careful study of a group of normal persons (1) that there is no evidence of rhythm in the changes in the numbers of the leukocytes (2) that at any time during the day there is a fall in the leukocyte count to the basal range after a rest of one half hour (3) that the apparent spontaneous alteration in the leukocyte count is slight, usually varying from 100 to 400 cells per cubic millimeter but occasionally reaching as high as 1 800 per cubic millimeter, (4) that in all instances of persons whom they studied there was a steady post meridian peak of the total leukocyte count between 12 00 noon and 3 00 P M , and finally that breakfast and a light lunch were not followed by evidence of a digestive leukocytosis Whether or not there occurs a leukocytosis attributable to the digestive processes is still unsettled The general opinion is that the changes in the total number of leukocytes during the day are independent of the ingestion of food The very extensive literature dealing with this subject is reviewed by Arneth and Ostendorf[4] and Carrey and Bryan[5]

Effect of Muscular Exertion on Leukocyte Count

It is clearly established that the leukocytes increase in numbers in the circulating blood following exercise and that the degree of leukocytosis is proportional to the severity and duration of the muscular exertion Reviews dealing with this topic have been published by Grawitz[6] Carrey and Bryan[5] and Sturgis and

Bethell[7] It has long been known that at the termination of a marathon race the leukocyte count may reach from 14 000 to 27 000 white blood cells per cubic millimeter of which 80 to 90 per cent are neutrophils Also immediately following a quarter mile race of less than one minute duration the white blood cell count may be 35 000 per cubic millimeter

Evidence that the height of the leukocyte count is proportional to the intensity and duration of the exercise is provided by Edwards and Wood[8] who noted an increase of nearly 300 per cent in the total leukocyte count of football players although the actual duration of play of any single player in 60 minutes in this sport is not over 8 minutes It was noted by these observers that after participating in one quarter of the game the average white blood cell count was 12 000 per cubic millimeter after one half 15 500 after three quarters, 18 000 and after having completed the entire game 23 000

It is generally accepted that the alterations in the leukocytes in the circulating blood following muscular exertion are due to circulatory shifts with the resultant liberation of sequestered leukocytes from unused or only partially used capillaries The leukocytes are known to be stored when the body is at rest in the capillaries of the various organs of the body such as the spleen liver lungs bone marrow muscles and glands of internal secretions

It should be recognized however that the increase in the white blood cells during exercise may be due to either a greater number of neutrophils or lymphocytes Apparently there are two reservoirs in the body one of which sequesters the neutrophils in the inactive capillaries and the other harbors a segregation of lymphocytes in the lymphatic system Cells of both types may be returned to the circulating blood following muscular exertion but in one person the lymphocytes may be swept into the circulation first while in another it may be the polymorphonuclear cells It is the commonly accepted opinion at present however that the lymphocytes usually respond to short severe bouts of exercise whereas following more prolonged exertion the leukocytosis is of the neutrophil type

Effect of Emotions on Leukocyte Count

It has been claimed that emotions may cause an increase in the white blood cell count but all observers are not in accord with this[9] In general it may be said that there is likely to be an increase in the number of leukocytes when the emotions of fear rage or excitement evoke a certain amount of physical activity which frequently is associated with an increase in the circulatory rate It is reported for instance by Milhorat Small and Diethelm[10] that a leukocytosis occurred in psychiatric patients in proportion to the emotional reaction but it would not be difficult to imagine that the latter paralleled the degree of physical exertion

Leukocyte Count in Pregnancy Labor and the Puerperium

Studies recently reported by Bethell Hartsuff and Farrell[30] indicate that the following changes occur in the leukocytes during pregnancy (1) the total leukocyte count remains at the upper limit of normal or slightly elevated throughout pregnancy with an average level of between 10,000 and 11 000 per cubic millimeter (2) there are usually minor changes in the total leukocyte count from month to month, (3) there is a persistent neutrophilia which does not exceed 70 per cent and one which reaches a peak during the seventh month of gestation and then undergoes a slight decrease (4) lymphocyte, eosinophil and basophil percentages are lower in non pregnant females, but the absolute values for these cells are but little affected during gestation

It is known that the total white blood cell count rises during parturition, there usually being an average increase in the white blood cell count of 2 000 per cubic millimeter after the onset of labor as compared with previous counts As labor progresses, the leukocyte counts rise to between 15,000 and 22 000 cells per cubic millimeter Usually the white blood cell count returns to normal by the seventh day of the puerperium Here also, it is thought that the contracting uterine muscle results in the sweeping out of the neutrophils from their sequestered locations in the viscera into the systemic circulation and thus accounts for the leukocytosis

Variations in Leukocyte Count with Age

At birth the leukocyte count normally varies between 15 000 and 25 000 per cubic millimeter with the figure being more commonly near the former On about the tenth day of life there is an abrupt fall in the leukocyte count to the vicinity of 12 000 to 14 000 per cubic millimeter, which is followed by a subsequent decline throughout infancy and childhood until the normal limits are reached The literature dealing with the leukocyte count in early life is given by Magnusson[31] At birth the neutrophils are the predominant white blood cell in the circulating blood but during the second week their numbers fall and they are exceeded by the lymphocytes These latter cells remain the predominating ones until about the fourth year of life, when they are surpassed in number by the neutrophils The eosinophils and basophils continue at a relatively uniform level throughout infancy and childhood, and their numbers are approximately equal to the adult values

Effect of Heat, Solar Radiation and High Altitude on Leukocyte Count

It is known that heat stroke and hyperpyrexia may be responsible for a striking increase in the white blood cell count The initial change however, induced

by an increased body temperature may be a transient leukopenia but this is followed soon by a leukocytosis The effect of hyperpyrexia induced by radiation with a wave length of 30 meters has been studied by Bierman[32] A febrile rise to 103° or 104° F was maintained in this way for a period of 3 to 4 days and the effects on the white blood cell count observed The initial change was a decrease in the total leukocyte count of about 25 to 30 per cent which occurred during the first or second hours of treatment This was due to a diminution of the number of neutrophils Following this there was a constant elevation in the number of leukocytes the maximum amounting to approximately 80 per cent above normal occurring between the sixth and ninth hour The magnitude of the response was proportional to height and duration of the temperature elevation but the greatest increase occurred several hours after the return of the body temperature to normal The highest leukocyte count recorded in these observations was 22 600 per cubic millimeter As the increase was due in large part to a greater percentage of neutrophils of which the unfilamented (staff) cells made up a large proportion it was concluded that the total leukocyte increase was attributable to an actual stimulation of the bone marrow and the production of new cells While this may be the case in part it should be kept in mind that the accelerated circulatory rate which invariably accompanies such a hyperpyrexia must contribute also something to the leukocytosis by causing a redistribution of the white blood cells in the body

The influence of high altitudes[33] ultraviolet light[34] and meteorological alterations[35] on the leukocyte count has been reported These changes usually are of relatively small magnitude and hence are ordinarily of little importance in clinical medicine

Normal Differential White Blood Cell Count

Although there are minor variations the normal number of the different white blood cells which are present in the circulating blood is well established The figures presented in the following table (Table I) taken from Wintrobe[36] gives the absolute and relative values of leukocyte counts per cubic millimeter of blood in normal adults

Errors in Determining Differential White Blood Cell Count — The possible errors in the differential white blood cell count should always be kept in mind when evaluating the figures of such a report It has been shown by Barnett[37] by the application of Bernoulli s theory that if 100 cells are counted in determining the differential formula and 50 per cent are neutrophils the standard deviation would be 5 per cent and the maximum error 15 per cent If the total number of cells enumerated were 400 instead of 100 these respective values are halved This observer concludes that at least 400 cells should be counted in order to

TABLE I

RELATIVE AND ABSOLUTE VALUES FOR LEUKOCYTE COUNTS IN NORMAL ADULTS PER CUBIC MILLIMETER OF BLOOD

Type of cell	*Per cent*	*Absolute number*		
		Average	*Minimum*	*Maximum*
Total leukocytes		7,000	5 000	10 000
Myelocytes	0	0	0	0
Juvenile neutrophils	3-5	300	150	400
Segmented neutrophils	54-62	4 000	3 000	5 800
Eosinophils	1-3	200	50	250
Basophils	0-0 75	25	15	50
Lymphocytes	25-33	2 100	1 500	3 000
Monocytes	3-7	375	285	500

obtain reliable results from the differential count The studies of Goldner and Mann[38] lead them to the opinion that satisfactory results may be obtained if 00 cells are enumerated They find, for example if this number of cells is counted when the polymorphonuclear cells are found to be 70 per cent, one may expect to find in 19 out of 20 times that the true proportion of these cells is somewhere between 63 6 and 76 4 per cent

Polymorphonuclear Leukocytes

It does not seem necessary to discuss here the morphological and staining characteristics of these cells and their progenitors the myeloblasts, myelocytes and metamyelocytes, as extensive descriptions are readily available elsewhere In regard to the neutrophil it may be said that this cell is one with a highly specialized primary function, namely, that of defense against infection in the body It is well equipped for this, as it has an extremely active amoeboid motion and the power of phagocytosis In addition it provides a proteolytic enzyme which plays a role in the liquefication of pus In health it is derived solely from the myelocytes of the bone marrow

Function of Polymorphonuclear Leukocyte — Of special interest is the motility of this cell which is associated with its most important function of ingesting and destroying bacteria It is the most active ameboid cell in the body When viewed on the warm stage, the cells commonly are seen actively undergoing changes in shape by the protrusion of blunt, tongue like pseudopodia Their rate of speed had been estimated to average 36 66 microns per minute at 37° C[39]

At the present time there is no evidence to indicate that the neutrophil has a physiological function It is recognized, however, that this cell constitutes the

first line of defense against various pathogenic agents namely certain bacteria fungi sphirochetes and possibly various other parasites Their usual method of operation is phagocytosis with intracellular destruction of the infecting organism The importance of the neutrophil in the defense of the body against infection is obvious in agranulocytosis when all of the neutrophils may disappear from the circulating blood At this time there is invasion of the tissues which normally harbor pathogenic organisms such as the throat vagina and rectum and when death occurs subsequently it is from septicemia in a high percentage of instances With the introduction of the sulfonamide drugs and penicillin a fatal outcome from such unresisted infection in this condition may be averted but prior to that time from 50 to 75 per cent of all these patients died

Although there is no conclusive positive proof for this statement there is suggestive evidence to indicate that the life of the neutrophil is of relatively brief duration probably only 3 to 5 days It has been observed in patients with agranulocytosis that these cells may disappear entirely from the circulating blood within 4 days after their number has begun to diminish[40] Following injury of the marrow with benzol it has been shown that the neutrophils have gone entirely from the circulation within 3 to 4 days[41] There is also evidence to suggest that one fifth of all neutrophils disappear from the circulating blood each day[42] which would indicate that the average length of life of such a cell is 5 days All indications are that these cells are removed from the circulation by the reticuloendothelial cells of the two great blood filters the spleen and the liver

Clinical Significance of Changes in White Blood Cell Count of Circulating Blood — The term leukocytosis as ordinarily employed means an increase in the total white blood cell count of the circulating blood above 10 000 per cubic millimeter As commonly used it implies that this results from an increased number of neutrophils but strictly speaking it might mean that it is due to a greater number of any one of the different types of white blood cells A preferable term to use when it is meant that the increase is due to neutrophils is neutrophilia but common usage has it otherwise Likewise the term leukopenia is employed to indicate that the total white blood cell count of the peripheral blood is below 5 000 cells per cubic millimeter and the decrease is due to a depression in the number of neutrophils A more acceptable term for such a condition would be neutropenia

In general it may be said that a determination of the total white blood cell count and the percentage of the neutrophils is of value in clinical medicine mainly for the following reasons (1) as an aid in clinical diagnosis chiefly in the infections and certain of the blood dyscrasias ( ) as a basis for a prognosis in certain infections

It is recognized that the most important causes of a neutrophilia (see Table II) are (a) certain acute infections such as pneumonia and many others as enumer

ated in the list given below, (b) infarction in any part of the body such as that associated with coronary thrombosis, (c) malignancy especially when the neoplasm is associated with tissue necrosis (d) the presence of "free" blood in some tissue of the body such as the meninges, between the coats of arteries in dissecting aneurysm or elsewhere, (e) in certain blood dyscrasias

TABLE II

THE MAIN CAUSES OF NEUTROPHILIA

1 Acute infections especially when due to streptococci staphylococci the pneumococcu meningococcus *B diphtheriae* and the colon bacillus A leukocytosis is seen also in acute rheumatic fever smallpox chickenpox anthrax cholera the plague actinomycosis and infection with *S icterohemorrhagica*
2 Severe acute hemorrhage The initial change in the peripheral blood which occurs following acute bleeding is a leukocytosis this often being apparent within 1 to 2 hours after the onset of the hemorrhage If there is bleeding into a serous cavity such as the peritoneal pleural subdural space or a joint the leukocytosis is more pronounced
3 Non inflammatory conditions as coronary thrombosis following surgical operations especially when there is extensive tissue injury and in association with malignant growths
4 Intoxications (a) exogenous such as poisoning with carbon dioxide mercury lead and other substances insects venom (the black widow spider) injections of foreign protein (after an initial leukopenia) (b) endogenous uremia ketosis eclampsia gout excessive hemolysis.
5 Chronic myelogenous leukemia and polycythemia rubra vera
6 Physiological leukocytosis following exercise in the newborn etc

As an aid in diagnosis, especially with relation to the type of infection, a determination of the white blood cell count is of value in suggesting the nature of the infection For example certain types of bacteria such as the pneumococcus cause a leukocytosis others such as the typhoid bacillus are associated with a leukopenia and virus infections as influenza, poliomyelitis and others evoke a leukopenia or at least fail to provoke a leukocytosis Rickettsial infections often are observed to have a slight leukocytosis, that is, in the vicinity of 12 000 to 14,000 per cubic millimeter

Leukocytosis in Association with Cardiac Infarction

Almost always within 4 to 5 hours in patients who have had a coronary thrombosis with infarction there follows a leukocytosis of from 12 000 to 20 000 per cubic millimeter or even higher in rare instances This usually persists for 7 to 10 days In association with this leukocytosis there is usually an increase in the percentage of neutrophils the total number reaching from 75 to 90 per cent There is some evidence to indicate that the degree and duration of the leukocytosis is proportional to the extent of the infarcted area

The presence of a leukocytosis in such a condition is of importance for at least two reasons First because it is of some assistance in the diagnosis as it is

one of the most commonly occurring manifestations of coronary thrombosis Furthermore a high leukocyte count and a non filamented count of over 30 per cent are suggestive of extensive infarction and hence a more unfavorable prognosis Second when a leukocytosis is considered in association with the observation that the pain of coronary thrombosis may be predominantly abdominal or even be limited exclusively to the upper abdomen it should be kept in mind that a condition closely simulating one which requires immediate surgical intervention is created In such instances only electrocardiographic evidence may point to the important fact that the symptoms are on a cardiac basis and an unnecessary and in some cases what would be a fatal operation is thus averted

Leukopenia

A leukopenia may be defined arbitrarily as a reduction in the total white blood cell count to 4 000 cells or less per cubic millimeter Most frequently this decrease is due mainly to a diminished number of granulocytes including neutrophils eosinophils and basophils When the leukocyte count is exceedingly low that is only a few hundred cells per cubic millimeter there is of course a diminution in all cells including granulocytes mononuclears and lymphocytes This condition is observed not infrequently in patients with agranulocytosis When this occurs almost all of the remaining cells are lymphocytes but even then the actual number of these cells per cubic millimeter is greatly reduced

The presence of a persistent leukopenia that is one which is present for more than a few hours is of importance to a physician for several reasons namely (1) It is characteristic of a certain number of infections such as typhoid fever brucellosis and virus diseases ( ) It is indicative of an ominous prognosis in certain infections which ordinarily evoke a leukocytosis (3) It is a common feature which serves to segregate a number of important blood diseases and hence is useful from a diagnostic standpoint (see section on Agranulocytosis)

Mechanism of Production of Leukopenia — According to Lawrence[13] a leukopenia may result from at least four different mechanisms as given in the following table

- I Diminished Production
  - 1 Inhibition
  - 2 Maturation arrest
  - 3 Aplasia of the bone marrow
  - 4 Infiltration of the bone marrow
- II Increased Loss
- III Accelerated Destruction
- IV Redistribution
  - 1 Retention in internal organs
  - 2 Between tissue and blood

It should be emphasized that, although the above table lists a number of different mechanisms by which a leukopenia may be produced, by far the most important is that of diminished production with its four different subdivisions The first division *inhibition of development* of the neutrophils without the omission of any of the essential steps in the process of development probably accounts for the leukopenia as seen in certain infections such as typhoid fever and overwhelming infections due to any other type of microorganism which ordinarily is associated with a leukocytosis as for example the pneumococcus A *maturation arrest* at the early myelocyte stage occurs in agranulocytosis with its multiple causes usually some type of drug such as aminopyrine the sulfonamides or thiouracil *Aplasia of the marrow* accounts for the leukopenia of aplastic anemia although in some cases of pseudoaplastic anemia, when the bone marrow does not exhibit aplasia but appears to be normal or even hyperplastic the leukopenia must be attributed to a maturation arrest *Infiltration of the bone marrow* with neoplastic cells is not an uncommon cause of leukopenia It is possible that the leukopenia of pernicious anemia should be included in this subdivision While under no circumstances can the cells in the bone marrow of a patient with pernicious anemia be regarded as neoplastic, nevertheless the cells of the red blood cell series predominate in the bone marrow and ' crowd out' the white blood forming elements

Redistribution of the white blood cells in the body with sequestration of a large number in the capillaries of the internal organs may remove a sufficient quantity from the peripheral circulation and hence produce a leukopenia This condition is the reverse of what is known to occur in patients who have a transient leukocytosis following exercise It is probable that the immediate but transient leukopenia which follows the injection of typhoid vaccine is based entirely on redistribution

A disturbance of the mechanism which controls the release of polymorphonuclear cells from the site of their formation or some disturbance between the distribution of the leukocytes in the bone marrow and the peripheral blood may account for the leukopenia which is observed in subleukemic leukemia

The reader is referred to the article by Lawrence[43] for a more detailed discussion of these processes

Recurring Acute Infectious Gingivostomatitis with Leukopenia — Three cases have been observed by me in recent years in which the outstanding clinical features were regularly recurring attacks of fever gingivitis and a striking leukopenia without recognizable cause The count frequently reached 2 000 to 4 000 cells per cubic millimeter and the neutrophils were usually from 10 to o per cent A condition in which the mouth symptoms were similar has been reported by Scott and his associates[44] under the name of 'acute infectious gingivostomatitis' In this group of cases, however no blood studies were reported In the patients I observed there were repeated attacks associated with the de

velopment of whitish exudate and superficial ulcerations on the mucous membranes of the mouth and throat chills fever and prostration Each febrile episode persisted from 5 to 7 days and this usually was followed by an interval of freedom from symptoms of to 3 weeks Many attacks with the intervals of comparative health, may follow in sequence The possibility that it may be due to an unidentified virus must be considered

Although the exact nature of the condition is not known it is well to keep in mind that a syndrome of possible virus etiology characterized by recurrent attacks of stomatitis fever and striking leukopenia may occur In some instances it may be confused with agranulocytosis

Chronic Granulocytopenia Caused by Excessive Splenic Lysis of Granulocytes — This syndrome was described first by Wiseman and Doan[46] in 1939 Since then a number of similar cases have appeared in the literature It is the opinion of Wiseman and Doan that the acute agranulocytosis appears as the result of excessive destruction of the granulocytes of the circulating blood in the spleen According to these observers the disorder is characterized by splenic enlargement peripheral granulocytopenia and myeloid metaplasia of the bone marrow The latter condition is regarded as compensatory in nature and the underlying mechanism is considered to be an abnormal hyperfunction of the spleen in phagocytizing essentially normal neutrophils Another possible explanation of the condition however is the assumption that there is some error in the development of the granulocytes and consequently they are removed selectively by the spleen It is reported that examination of the spleen in such patients shows a large number of neutrophils being engulfed and destroyed by phagocytes

The diagnosis of the condition appears to rest on the presence of a hyperplastic or normal bone marrow with a striking diminution of granulocytes in the circulating blood The syndrome has spontaneous remissions and recovery is reported following splenectomy Certainly extreme care should be taken to differentiate the disorder from other leukopenic states before such a radical measure as splenectomy is undertaken

Differential Diagnosis of Conditions Associated with Leukopenia — When it is observed that a patient has a white blood cell count persistently below 4 000 per cubic millimeter it represents a finding which may be exceedingly helpful from the standpoint of diagnosis Careful attention therefore should be given to the conditions responsible for a leukopenia It must be admitted however that some normal persons and also patients with various diseases may have a white blood cell count below 4 000 per cubic millimeter for some unknown reason and hence it must be conceded that after a careful study it is not always possible to state the cause of such a low white blood cell count Nevertheless a leukopenia always should be considered as a diagnostic finding which may be of the greatest importance

In general it is possible to divide those conditions which are associated with a leukopenia, into those likewise having an anemia and those in which the red blood cell count and the hemoglobin levels are normal or only slightly below normal If an anemia is present, the erythrocytes are almost always either normal or increased in size and their hemoglobin content usually is within normal limits In other words the associated anemia is usually normocytic or macrocytic and normochromic in type Among those conditions in which an anemia occurs with a leukopenia are subleukemic leukemia, pernicious anemia aplastic anemia Banti s disease Felty s syndrome and Gaucher s disease In some instances patients with Hodgkin s disease and lymphosarcoma also may have an anemia associated with a low white blood cell count It should be kept in mind however that in any condition, in which the roentgen ray is utilized as a therapeutic agent it may be responsible for a low white blood cell count

Of these forms of blood dyscrasia associated with a leukopenia the following 3 are of the greatest importance subleukemic leukemia pernicious anemia and aplastic anemia The diagnosis of subleukemic leukemia often causes considerable confusion, but such a diagnostic error would not occur as frequently if the condition were kept in mind as a possibility whenever a leukopenia was observed in association with a normocytic or slightly macrocytic anemia If in addition 5 per cent or more of the white blood cells in the circulating blood were found to be immature forms the diagnosis should be suggested immediately Often confirmatory proof of the presence of the disease is obtained by the presence of splenomegaly or lymph node enlargement or both It is usually possible to secure positive evidence of the condition from sternal puncture, by which means a leukemic infiltration may be demonstrated in the bone marrow The diagnosis of subleukemic leukemia is overlooked often This group of patients is a sizeable one among those referred to the Simpson Memorial Institute with the statement that they have a severe anemia of obscure etiology

The leukopenia of pernicious anemia is discussed fully in the section in the next chapter dealing with this blood disease It may be stated here, however that a leukopenia is one of the most constant diagnostic findings observed in this disease when the patient is seen in a relapse and with an anemia below 3 or million red blood cells per cubic millimeter If a patient were suspected of having true pernicious anemia and a leukocytosis was observed it would cast considerable doubt on the diagnosis It would not however completely eliminate it for consideration This is because in some instances nucleated red blood cells are enumerated erroneously as leukocytes in the counting chamber, and also a leukocytosis may actually occur in patients with pernicious anemia at the beginning of a spontaneous or therapeutically induced remission If these possibilities can be eliminated then it may be said that a leukocytosis is rarely, if ever, observed in patients with the disease

A neutrophilic leukopenia often of striking extent is observed constantly in the blood of patients with aplastic anemia This change is associated always with a reduction in the other elements which arise from the bone marrow namely the erythrocytes and the blood platelets

It should be emphasized that a leukopenia is present commonly in the rare condition included under the term of lupus erythematosu disseminata which often presents a difficult diagnostic problem It should be considered in any patient with vague aches and pains fever erythematous macules or papules or the skin urinary changes and a persistent leukopenia with a slight to moderate hypochromic anemia in the advanced stages of the lupus disease

There are many conditions which are characterized by a leukopenia without other important changes in the red blood cells It should be kept in mind that practically all virus infections are unaccompanied by a leukocytosis and in some instances there may be a pronounced leukopenia Also in patients with an overwhelming infection there may be a leukopenia in a bacterial infection which ordinarily is associated with a leukocytosis

There are 2 acute conditions which should be given special attention when a leukopenia is present without an anemia They are agranulocytosis and infectious mononucleosis The former condition usually is due to some drug or physical agent among which the following are the most important aminopyrine the sulfonamides gold thiouracil arsenic radium and the roentgen ray This condition is fully discussed in the chapter dealing with that disease and also in the chapter following this one Only two additional points will be made here When a leukopenia of this type is present not only is there a pronounced decrease in the total white blood cell count but also the percentage of neutrophil is greatly reduced usually below 20 per cent and it is not rare to have them entirely disappear from the circulating blood This observation is of importance because it assists in differentiating a leukopenia due to agranulocytosis from that due to an overwhelming infection In the latter condition the total white blood cell count may be low but the neutrophils usually are in the vicinity of 50 per cent and rarely is the percentage as low as is seen in true agranulocytosis Furthermore it is important to appreciate that a pronounced reduction in the number or complete disappearance of neutrophils is most likely due to agranulocytosis for then (1) the causative drug may be eliminated and (2) the proper treatment with large doses of penicillin may be instituted usually with satisfactory results

Infectious mononucleosis is another acute disease which should be kept in mind when a patient is observed with evidence of an acute infection and a leukopenia is found to be present It is not usually appreciated that in the first week of this disease a leukopenia is observed in at least one half of the cases and the characteristic infectious mononucleosis cells may not appear until later In

such a situation the condition may present further difficulty in recognition because in the first week of the disease the heterophile antibody reaction often is not yet positive

The Relation of the White Blood Cell Count to Prognosis

In any given infection a determination of the total white blood cell count and the differential formula with a classification of the neutrophils as determined by the nuclear shape Arneth classification and certain changes in the cytoplasm give information which is of special value from the standpoint of prognosis There are three types of data which are of assistance in formulating a prognosis (1) The total number of neutrophils may be considered as a measure of the complete response of the bone marrow to any given infection (2) The percentage of young neutrophils as determined by the appearance of their nuclei, may be accepted as an index of the effort being made by the bone marrow to combat the infection (3) The percentage of neutrophils with basophilic granules in the cytoplasm may be taken as an index of the severity of the infection which is active in the body

Total Leukocyte Count

It is generally accepted that the total leukocyte count may be considered as one measure of prognosis in any given case This is especially true if there is a leukopenia in the presence of an infection which ordinarily evokes a leukocytosis For example if a patient obviously is critically ill with pneumococcus pneumonia and the leukocyte count is below 6 000 per cubic millimeter, this in itself is indicative of an ominous outlook It is also true that in patients with an infection which ordinarily is not associated with a leukocytosis the level of the white blood cell count likewise gives some indication of the prognosis because in severe infections a pronounced leukopenia may develop This occurred in one patient of mine with typhoid fever in whom the total white blood cell count fell to 300 per cubic millimeter just prior to death

Although the information is not as reliable it is suggestive that, when an unusually high white blood cell count develops in any given patient one at a level which might be considered as a hyperleukocytosis such as 50 000 or more the outlook is less favorable Not only is this verified by clinical experience but also it is reasonable to assume that any infection which provokes a leukocytosis of such an extent must be of a virulent character

Classification of Various Types of Polymorphonuclear Leukocytes from Their Nuclear Structure

Since the earliest classification of the neutrophils by Arneth[46] in 1904 into five main divisions the importance of estimating the age of these cells has been emphasized To Arneth must be accorded the credit for elaborating the principle that the nucleus of the neutrophil as it develops from the youngest or myelocyte stage in the bone marrow to the oldest cells of the circulating blood is first circular in shape then is indented and finally divides into lobes which are connected by a narrow filament It is possible therefore to subdivide the neutrophils into five groups according to age as determined by the changes in the nucleus On this basis Arneth introduced the term shift to the left which means an increase in the number of young neutrophils and shift to the right which indicates that there is an increase in the older cells

This index has been simplified until now in my opinion the necessary information may be obtained by dividing all neutrophils into two main classes, namely the segmented and non segmented forms The segmented or non filamented types are identified easily because there is no slender filament between the lobes but there is a nucleus which is round or shaped like a horseshoe Normally the juvenile non filamented or non segmented forms make up from 3 to 5 per cent of all the neutrophils in the circulating blood In brief it may be stated that an estimation of the percentage of cells which are of the non segmented type is an index of the effort which the bone marrow is making to overcome an infection If these neutrophils reach 50 per cent or higher it may be assumed that the bone marrow i exerting every possible effort to combat the existing infection Such a change would represent a shift to the left as many young forms are present If the older forms predominate there is a shift to the right

Qualitative Changes in Cytoplasm of Neutrophils

Basophilic granulations or ' toxic granules may be described as coarse dark blue irregularly shaped granules in the cytoplasm of the neutrophils which are accepted as the evidence of infection in the body If the percentage of neutrophils containing such granules is determined this may be considered as an index of the severity of the infection in a patient When such an estimation is made daily it is possible to deduce the trend of the severity of the infection with a rough degree of accuracy In some instances only 8 to 10 per cent of the neutrophils are observed to contain such granules whereas in others they are present in all of the neutrophils of the circulating blood A progressive increase in the percentage from day to day may be accepted as convincing evidence of an active infection which is increasing in severity

It should be kept in mind, however, that the basophilic granulations in the cytoplasm of neutrophils of the circulating blood are not limited to the infectious processes They may occur, for example, in various other conditions including reactions following incompatible blood transfusions and following intensive roentgen ray exposures employed in the treatment of malignancy and myelogenous leukemia As these granules may be detected in the cytoplasm of the young neutrophils in the bone marrow, it is almost certain that the change usually occurs at this site

When toxic granulations are present in the cytoplasm of the neutrophils they are accompanied often by other evidences of degenerative changes, and it is likely that they are the result of the same "toxic" influences These alterations are bluish staining areas and vacuolization which must be accepted as having the same clinical significance as basophilic granulations In resume of what has been stated concerning the changes in the circulating leukocytes, especially in relation to prognosis, the following summary may be given

If a patient has an infection with a white blood cell count of 20 000 per cubic millimeter and a neutrophil percentage of 80 to 85 per cent, this should be interpreted as an entirely satisfactory response of the bone marrow In addition if the percentage of young or non filamented cells is 50 or more, it indicates that the marrow is making a satisfactory effort to resist the infection If, furthermore 50 per cent or less of the neutrophils show basophilic granulations and the percentage is decreasing each day, then it may be assumed that the severity of the infection is not unusual and is rapidly becoming less If these alterations were associated with clinical evidences of improvement, then one might confidently say that the prognosis was good and the condition of the patient was satisfactory

On the other hand, the reverse of these changes would clearly indicate a poor prognosis For example if the patient with a pneumococcus pneumonia, which ordinarily is associated with a leukocytosis, has a leukopenia of 5 000 white blood cells per cubic millimeter or less the prognosis is much less favorable If in addition the number of young neutrophils is 50 per cent or more it would indicate that this poor response is extant despite the satisfactory effort on the part of the bone marrow Furthermore, if more than 50 per cent of the neutrophils contained basophilic granulation and the percentage was increasing each day this likewise is strongly suggestive of a poor prognosis

THE LYMPHOCYTE

The lymphocytes make up from 25 to about 30 per cent of all of the white blood cells in the circulating blood It is known that these cells are derived from lymphatic tissue in various parts of the body such as the lymph nodes, soli

tary lymph nodes of the intestine Peyer's patches the thymus tonsils and possibly the bone marrow Two types of lymphocytes are recognized readily in the circulating blood the small lymphocytes which measure from 8 to 10 microns in diameter and the large lymphocytes which vary from 10 up to 20 microns in diameter It has not been demonstrated conclusively that there is a true maturation cycle of the lymphocytes as is the case in myeloid cells but it has long been accepted in clinical medicine that the large lymphocytes are young and the small lymphocytes are older cells

According to Maximow[17] there seems to be no secure basis for the discussion of the functions of the lymphocytes It is known that the lymph nodes are highly active in combating infection and it is possible that the lymphocyte in some as yet undiscovered manner contributes importantly to this essential activity of the body The development of a lymphocytosis in diseases as pertussis and infectious mononucleosis suggests strongly that these cells possess some ability in combating such infections but their exact rôle is unknown at present

In recent years there has been considerable speculation concerning the relation of the lymphocytes to various metabolic functions such as the formation of certain enzymes but these claims have not been substantiated

The following are the causes of a lymphocytosis

1 Physiological in infancy

2 In certain infections as pertussis rubella mumps infectious mononucleosis and undulant fever

3 Lymphocytic reactions to pyogenic infections in childhood

4 During convalescence from any infection

5 Tuberculosis when resistance is good

6 In lymphatic leukemia

7 In acute or chronic infectious lymphocytosis of childhood

8 In exophthalmic goiter

It should be kept in mind that occasionally there is a reduction in the number of lymphocytes or a lymphopenia which may be of some diagnostic importance A lymphopenia may be defined as existing when the total number of lymphocytes in the circulating blood are less than 1 000 per cubic millimeter The following conditions may be associated with such a state

1 Acute infections with leukopenia

2 Advanced Hodgkin s disease

3 Tuberculosis when the resistance is poor

4 Excessive irradiation

5 Agranulocytosis in the advanced stages at such times the total white blood cell count may be only a few hundred

6 Leukemia other than lymphatic

7 Subleukemic lymphatic leukemia

The Monocyte

The monocytes compose between 3 and 5 per cent of all the circulating white blood cells They are somewhat larger than the lymphocytes being about the size of the eosinophil, that is measuring 12 to 20 microns in diameter Usually there is no difficulty in differentiating between a monocyte and a lymphocyte but it must be admitted that in almost every specimen of blood examined there are some which have suggestive characteristics of both cells In such instances it is probably more correct to consider these as lymphocytes

The origin of the monocyte is in dispute It is claimed by Naegeli, Ferrata and Sabin Doan and Cunningham that the monocyte is derived from the monoblast This cell in turn is considered by some to arise from a histiocyte On the other hand Bloom[18] contends that the monocytes are neither myeloid nor lymphatic tissue cells but they have several sources of origin It is his opinion that the most clearly recognized ones are the lymphocytes or the hemocytoblasts or at least cells which cannot be differentiated from lymphocytes It is maintained stoutly by Bloom[18] that the idea of the origin of this cell from a specific "monoblast" that is a free cell morphologically different from a hemocytoblast (i e a myeloblast or lymphocyte), has not been demonstrated and furthermore according to this observer such a view has been proved untenable on the basis of the evidence so far advanced Despite this statement however, in my opinion the idea that the monocyte arises from a specific monoblast is the most helpful one for the clinician to assume at the present time

The function of the monocyte is not recognized clearly at present, although all agree that it undoubtedly has the power of phagocytosis, and hence that it is probably concerned with resistance to chronic infection and perhaps some phases of acute infection Furthermore it is known that these cells are capable of developing into macrophages and fibroblasts Studies[19] by Sabin have indicated that the monocyte is related to the formation of the tubercle, as it has been shown that the lipoids of the tubercle bacillus are phagocytized by this cell with a resultant degradation and transformation into epithelioid cells It is considered that the activity of the cells in this manner results in an increase in their number in the circulating blood which is regarded as an unfavorable sign by some There is also evidence to suggest that in subacute bacterial endocarditis the monocytes constitute one form of resistance against this infection This is supported by the not uncommon observation that monocytes may ingest erythrocytes or even neutrophils in the blood of patients with this disease

In general it may be stated unequivocally that an estimation of the number of monocytes in the circulating blood is not of great practical assistance in the diagnosis or prognosis of diseases in clinical medicine This is because the change in the number of monocytes usually is small too frequently the differential

count is based on the enumeration of an inadequate number of cells and the inexpert sometimes will confuse monocytes with lymphocytes

The list of conditions which may be associated with a monocytosis is as follows

1 *Chronic infections as brucellosis and subacute bacterial endocarditis*
2 Tuberculosis when the condition is advancing
3 *Rickettsial disease as typhus and Rocky Mountain Spotted Fever*
4 Hodgkin s disease sometimes
5 *Monocytic leukemia*
6 Tetrachlorethane poisoning
7 *In the recovery phases of agranulocytosis*

White Blood Cell Count in Pulmonary Tuberculosis

The exact value of the total white blood cell count in the diagnosis and prognosis of pulmonary tuberculosis has yet to be evaluated on a large scale The extensive and careful studies of Medlar[50] Muller[51] and others suggest that information of value relating to this disease might be obtained from a careful study of the percentages of the various white blood cells in the circulating blood

It is considered by Medlar[50 5] that (1) The neutrophil plays the chief role in the formation of tuberculous abscesses and the extension of tuberculosis ulcers (2) The lymphocyte predominates when a tuberculous lesion is healing (3) The monocuclear leukocyte is the chief cell of tubercle formation (4) The total leukocyte counts by themselves indicate roughly the volume of dearranged tissue with which the leukocytes have to cope

It is the opinion of Crawford[54] that the evaluation of these 4 factors enables one to determine the statu of the tuberculous process and to decide whether the leukocyte picture indicates a nonseptic or healing process a hyperplastic process with the formation of new tubercles which are not undergoing abscess formation or extension of tuberculous ulcers It is considered that an unfavorable situation due to sepsis is indicated when the neutrophils rise above 65 per cent and the lymphocytes are below 25 per cent If in addition at this time the monocytes become increased in numbers the process is even more unfavorable New tubercle formation as suggested by an increase in monocytes in the absence of abscess formation is more favorable Healing is suggested by an approximation of the percentages of neutrophils and lymphocytes with little or no evidence of tubercle formation as indicated by a monocyte percentage of below 10

In the interpretation of the relation of the percentages of the various white blood cells in the circulating blood in tuberculosis the greatest stress is placed by Medlar[5] on the ratio between the neutrophils and lymphocytes as follows

$$\text{Neutrophils Lymphocytes or } \frac{N\%}{L\%}$$

He contends that a ratio of 1 1 indicates healing of the tuberculosis lesion When N L reaches 60% 30% or 2 1 it is indicative of a lesion in which the trend is toward abscess formation In summary it may be said that a ratio of 1 1 is ideal one of 2 1 suggests the beginning of a process which is unfavorable and an increase to 3 1 or 4 1 represents a still more unfavorable process The entire subject relating to the changes in the circulating white blood cells to the underlying pathological tuberculous process in the lungs has been comprehensively reviewed by Muller[51]

Eosinophils

These cells are derived from the myeloblasts of the bone marrow and pass through the myelocyte stages as do the neutrophils They have a tendency to be somewhat larger than the average neutrophil and the nucleus commonly is bilobate The characteristic morphological feature, of course is the conspicuous coarse, circular granules which crowd the cytoplasm and have an affinity for the eosin dye In some instances, if Wright's stain does not have the proper pH reaction the granules of the neutrophil may assume a reddish tint and be confused by the novice with true eosinophilic granules This mistake would never be made by an experienced observer as it is always possible to distinguish the larger eosinophilic granules from the much smaller neutrophilic one on the basis of size alone

The exact functions of the eosinophil are not entirely known, although it is commonly accepted that an important one is concerned with the defense of the body against animal parasites It is not however, considered to be a phagocytic cell which is active against bacteria or their products The eosinophilia which is known to exist in allergic states, at once suggests the importance of these cells in such conditions, but the precise nature of this relationship at present is obscure Our deficiency of knowledge concerning the function of this cell has been epitomized by Bunting[54] who in 1928, made the following statement "The function or functions of the cell and its exact life history must be left as a matter of uncertainty at the present time' Nothing has been accomplished since then to indicate that this statement should be altered

Eosinophilia in Clinical Medicine

Despite the fact that our fundamental knowledge concerning the functions of the eosinophil is vague there is no question in the mind of any experienced clinician concerning the high diagnostic value of an increase in the number of these cells in the circulating blood It is a finding which always demands an explanation The presence of an outspoken eosinophilia in any patient that is one exceeding

3 per cent or an absolute number of eosinophils greater than 300 per cubic millimeter should arouse at once the suspicion that trichinosis may be the underlying cause although of course such an eosinophilia might be associated with a number of other disorders The following conditions may be associated with an eosinophilia

1 Parasitic infestations especially with trichinella ecchinococcus and intestinal worms

Skin diseases of all types including those due to drugs and especially, pemphigus and dermatitis herpetiformis

3 Allergic phenomena as allergic rhinitis bronchial asthma urticaria angioneurotic edema and some cases of food allergy

4 Certain unrelated conditions as scarlet fever rheumatoid arthritis periarteritis nodosa Loeffler s syndrome dermatomyositis erythema multiforme and neoplasms involving serous surfaces or bones

5 During convalescence from an acture infection accompanied by a neutropenia

6 Following the ingestion of a liver diet in patients with pernicious anemia

7 Following irradiation

8 As an unexplained familial anomaly

From the standpoint of differential diagnosis it should be kept in mind that an eosinophilia occurs most commonly in association with trichinosis allergic conditions and infestation with intestinal parasites The presence of such a finding in the blood however may be exceedingly useful in directing attention toward some obscure disease as periarteritis nodosa with which it is commonly associated and to such rare conditions as dermatomyositis

Experience in World War II has increased our interest in tropical disease and the various changes which may occur in blood in these conditions The importance of this is well illustrated in a recent study of Australian soldiers by Lowe[55] who found that the 3 common helminths observed in the stools of soldiers of the tropics were hookworm *Trichocephalus trichuris* and *Strongyloides stercoralis* Any one of these infestations may account for an eosinophilia which in some instances is pronounced It was found also by this observer that some patients who were convalescent from malaria but in whom no helminth infestation could be detected might also have an eosinophilia with an average number of eosinophils of 250 per cubic millimeter although in some instances it reached a maximum of 1 350 cells per cubic millimeter Of great interest in the group of patients studied by Lowe[55] were those with unexplained eosinophilia In these patients the number of eosinophils ranged from 1 000 to 3 000 cells per cubic millimeter which would mean an eosinophilia of between 10 and 30 per cent if the white blood cell count was 10 000 per cubic millimeter Undoubtedly in a person who has lived

recently in the tropics, such a finding is almost unequivocal evidence of the presence of some variety of intestinal parasite

Of clinical interest is Loeffler s syndrome, which may be defined as a transient pulmonary infiltration associated with an eosinophilia of the circulating blood[56] The condition usually is characterized by attacks of asthma with cough, the occurrence of an eosinophilia varying from 10 to 60 per cent with a slight leukocytosis the presence of a mild fever and an elevated sedimentation rate Physical signs in the lungs may be slight or absent, but the roentgen rays demonstrate pulmonary infiltrations often of unanticipated extent, most commonly in the lower lung fields It is characteristic for them to disappear rapidly and not to form cavities An excellent review dealing with this condition is given by Hoff and Hicks[57] It is now generally considered that the etiological basis for the condition is one of allergy

The Basophils

These cells are recognized easily because they contain coarse irregularly shaped granules which have an affinity for basic dyes as the blue of Wright s stain and hence are designated very properly as basophils There is not the slightest evidence to indicate what the function of these cells is or the clinical significance of changes in their number in the circulating blood The statement by Bunting[54] that even such a small number in the peripheral blood as the normal 0 4 to 0 6 per cent means that 200 000 000 are present in the circulation at any given moment is impressive Surely a cell which is present in such large numbers must be there for a useful purpose

Never has an increase in these cells been of important significance in clinical medicine in my experience with the possible exception that they are increased almost always in myelogenous leukemia In this condition however, the other characteristic changes in the blood usually are so conspicuous that additional diagnostic assistance is not needed According to Bunting[54] there is an increase in basophils in myelogenous leukemia polycythemia Hodgkin s disease chronic inflammation of the accessory sinuses and in smallpox and chickenpox It has been reported[54] that there is an increase in basophils along with eosinophil following the injection of foreign protein, but the response of these cells is said to be less regular than the eosinophils

Plasma Cells

Rarely a few of these cells may be observed in the normal circulating blood but when present to any extent they should excite the suspicion that the patient has either a plasma cell leukemia or the closely allied condition of multiple myeloma The typical plasma cell may be described as egg shaped and one with an

eccentrically placed nucleus which characteristically contains chromatin arranged in the shape of spokes of a wheel

The so-called multiple myeloma cell which resembles a plasma cell more closely than any other cell in the body does not usually have this spoke like arrangement of the chromatin The cytoplasm of the cells when stained with Wright s stain is greenish blue in color

There is no information available which indicates conclusively the origin of plasma cells but the current belief is that they arise either from lymphocytes or what is more likely from some type of connective tissue cells The function of the plasma cell is totally unknown but various vague hypotheses have suggested to the effect that they are secretory elements that they are related to the formation of defense substances or that they in some as yet obscure manner absorb and dispose of some of the products of tissue metabolism

Blood Platelets

When viewed in the fresh unstained state the blood platelets are seen as small colorless moderately refractile bodies which are circular in outline often with slightly irregular edges or they may appear as having oval or various bizarre shapes They average between 2 and 4 microns in diameter These elements of the circulating blood should be regarded as cellular particles for they are without a nucleus and it is accepted generally that they arise as bits of disconnected tissue from the cytoplasm of the megakaryocytes in the bone marrow When stained with Wright s stain they appear to have a central granular portion which stains reddish purple and a body which gives the impression that it is composed of a hemogenous light blue staining material Occasionally giant platelets may be present in the circulating blood These are seen in some patients with myelogenous leukemia and with polycythemia

It has long been recognized that the platelets are intimately concerned with the coagulation of the blood and it is agreed generally now that they accelerate this process There is not however entire accord among students of the problem concerning the exact role of the platelets in this process It seems safe to state that they provide something (thromboplastin cytochrome) which is necessary to the normal clotting process and furthermore it is recognized that in some way the platelets are responsible chiefly for the retraction of the clot In the former function it is generally thought that the platelets contribute something which expedites the change from prothrombin to thrombin In any event clinical experience has shown that when a deficiency of platelets is present the patient is likely to have an abnormal tendency to bleed Under these circumstances the bleeding time often is prolonged greatly and the clot when it forms will not retract normally

The number of platelets is said to be about 250 000 per cubic millimeter with a normal variation between 200,000 and 400 000 per cubic millimeter, but this figure varies with the method of enumeration which is employed With a properly prepared and stained blood film a skilled observer can probably estimate more accurately the number of platelets than can be determined by the actual methods of counting at least when an inexperienced technician is responsible for the latter

Decrease in the Number of Platelets

A deficiency of platelets is the outstanding feature of the blood in thrombocytopenic purpura In the idiopathic variety the essential lesion is a striking decrease in the number of blood platelets, due to an unknown cause, to the point where they may disappear entirely from the circulating blood With this is associated abnormal bleeding from the mucous membranes and into the skin a prolongation of the bleeding time usually a normal coagulation time and failure of the clot to retract The idiopathic type of thrombocytopenic purpura is called purpura hemorrhagic or Werlhof's disease Secondary thrombocytopenic purpura is the condition which follows a reduction in the platelets from known causes

Secondary thrombocytopenic purpura is known to be associated with the following conditions

1 With various blood diseases such as leukemia, aplastic anemia and pernicious anemia

2 As a result of various types of infections as meningococcus infections typhoid fever septicemia typhus fever, miliary tuberculosis smallpox, subacute bacterial endocarditis

3 In allergic states of these conditions drug allergy is the most important Chemical substances which may be responsible for this are organic arsenicals (arsphenamine) sedormid gold preparations, benzol, sulfonamide drugs quinine and possibly ergot bismuth phenobarbital iodides and others Food allergy is undoubtedly important but how significant it is in patients with purpura is a point which must be left for future investigations

4 In cirrhosis of the liver

5 In cancer bone marrow metastases especially in cancer of the stomach multiple myeloma or any malignant process which may metastasize to the bone marrow

Increase in the Number of Blood Platelets

Such an increase may occur but it is not as important in clinical medicine as a thrombocytopenia An increase, thrombocytosis, is observed in normal per

sons after exercise and immediately following the injection of epinephrin In both instances this may be due to a redistribution in a manner similar to that alteration which is responsible for a transient increase in leukocytes following exercise During the active phase of some suppurative infections and also in rheumatic fever there may be an increase in the number of platelets There is a thrombocytosis following surgical operations especially splenectomy in association with trauma such as fractures and in asphyxiation It is noted regularly that acute hemorrhage may be associated with a pronounced increase in the number of platelets but this is not usually true of chronic hemorrhage in fact the reverse namely a decrease in the number of platelets may be observed in the latter condition In Hodgkin s disease, polycythemia and myelogenous leukemia there may be a thrombocytosis

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CHAPTER XVI

THE ANEMIAS

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Introduction

Definition of Anemia — An anemia may be defined as a diminution in the concentration of hemoglobin or erythrocytes of the circulating blood or both below the normal accepted values with respect to age and sex While this is an accurate definition of almost all of the anemias as encountered in clinical medicine changes in the blood volume occasionally introduce another factor which must be taken into account when the concentration of both the hemoglobin and the erythrocytes of the circulating blood is considered Only two examples will be given to illustrate how in exceptional instances it may exert an influence of some importance In the anemias of pregnancy for instance the actual number of erythrocytes and the amount of hemoglobin in the circulating blood usually is normal throughout this state When the red blood cell count is done by the usual technic however especially after the sixth month of pregnancy, it is found frequently to be in the vicinity of 3 5 millions per cubic millimeter and the hemoglobin concentration may be as low as 10 grams per 100 c c of blood (64 per cent) These changes do not indicate that an actual anemia is present as they may be attributed to the effect of dilution associated with an increase in the amount of blood plasma which is known to occur up to 6 per cent in normal healthy pregnant women during the last trimester of gestation On the other hand in shock where there is often a striking reduction in the total blood volume with a decrease of the total blood volume to as much as 50 per cent or more of normal an actual anemia which may be present is not apparent This is because although the number of erythrocytes in the entire body is much less than normal a sample of blood taken from the ear or finger due to the increased concentration of the blood resulting from the loss of plasma gives no evidence of an anemia For example in a person with an extensive hemorrhage although there may have been a large amount of blood lost the subsequent contraction of the blood volume with concentration of the erythrocytes does not give a clear indication of the presence or severity of the anemia While these exceptions to the definition given above should be kept in mind usually they do not interfere greatly with the interpretation of the levels of the hemoglobin or red blood cell count as ordinarily determined in clinical medicine with reference to the presence or degree of an anemia

Classification of the Anemias

The anemias may be classified according to several different criteria but the most useful is to employ as a basis (1) the mechanism of the production of the anemia and (2) a morphological classification which is based on the volume and hemoglobin content of the erythrocytes Both serve a useful purpose

D Depression of erythrocytosis
1 In association with chronic infection especially in the urinary tract, the bronchi the pelvis bone (osteomyelitis)
2 Malignancy while the cause of anemia in association with malignancy may be due in part to chronic hemorrhage infiltration of the bone marrow or diminished food intake apparently it may be accounted for also by depression of the bone marrow due to a toxic effect of the neoplasm

Morphological Classification

By means of the determination of the mean corpuscular volume and the mean corpuscular hemoglobin concentration it is possible to divide all anemias into several distinct types This is useful on account of the therapeutic indications at least for the two most important forms of treatment namely liver and iron as these forms of therapy are indicated clearly by the size and hemoglobin content of the cells Liver is effective only when there is a macrocytic anemia whereas iron exerts its effects only when hypochromia is present

Microcytic Anemia — All anemias may be divided into the microcytic normocytic and macrocytic varieties depending on the size of the erythrocytes It is accepted generally that the normal red blood cell size is between 86 and 95 cubic microns and any measurement of cell size which is below 86 cubic microns is regarded as a microcytic anemia Most frequently the cell measurement in anemias of this type is in the vicinity of 65 to 70 cubic microns although I have seen it as low as 45 cubic microns Such an anemia is associated commonly with hypochromia This condition is designated arbitrarily as one in which the mean corpuscular hemoglobin concentration is below 30 per cent and often it may be as low as 26 or 27 per cent In the presence of a microcytic hypochromic anemia at once the diagnosis of an iron deficiency anemia should be suggested This is an important type of anemia to recognize because the response to adequate iron therapy usually is immediate and gratifying The only type of hypochromic microcytic anemia which does not respond to this form of medication as far as I know is Mediterranean or Cooley s anemia

Macrocytic Anemia — A macrocytic anemia is one in which the mean corpuscular volume is 96 cubic microns or greater In such anemias the mean corpuscular hemoglobin concentration is usually about 30 per cent or higher and hence such an anemia is said to be a macrocytic normochromic anemia *

* Because the color index may be greater than one and cells in certain anemias such as pernicious anemia may appear darker than normal the erroneous use of the term hyperchromic anemia has been employed at times This term is incorrect because the red blood cells are never supersaturated with hemoglobin When the hemoglobin is increased in any given cell it is only in proportion to the greater size of the cell The dark appearance which may be present is due to the increased thickness of the cells as seen in some of the hemolytic anemias and in pernicious anemia The term hyperchromic should not be employed.

Classification Based on the Mode of Production of the Anemia

All anemias may be divided into two main groups, namely, those which depend on the excessive removal of red blood cells from the circulating blood (hemorrhage and hemolysis) and those in which there is impairment, for one reason or another, of the rate of production of red blood cells This classification may be presented as follows

I Increased rate of removal of the erythrocytes from the circulation

A Hemorrhage either acute, chronic or recurrent

B Hemolysis which may be due to drugs infection an incompatible blood transfusion or arising from unknown causes Such anemias may be classified into (a) acute, (b) chronic, (1) acquired, or (2) congenital

II Decreased rate of red blood cell formation The lack of certain specific substances may prevent the normal rate of red blood cell formation due to slowed maturation When this occurs, as the red blood cell destruction proceeds at a normal or in some instances an accelerated rate, the erythrocyte count in the circulating blood must fall

A Deficiencies resulting in decreased red blood cell formation

1 Erythrocyte maturing factor (E M F), "liver principle"
2 Iron
3 Protein, as in the anemias of pregnancy
4 Vitamins certain fractions of the B complex
5 Hormones thyroid adrenal

B Destruction of erythropoietic cells in the marrow (aplastic anemia) Characteristically in aplastic anemia the marrow is destroyed and replaced by fat In more recent years, however in some patients who present the characteristic clinical picture of aplastic anemia it has been found that the bone marrow is normal or even hyperplastic Such types of aplastic anemia have been designated as pseudoaplastic anemia True aplastic anemia may be subdivided into the following groups

1 Due to chemicals such as benzol, gold and possibly, the sulfonamides
2 Irradiation with the roentgen ray, radium or radioactive elements
3 "Idiopathic", arising without discoverable cause

C Myelophthisic or displacement of the erythrocyte forming tissue by foreign cells as in leukemic infiltration, infiltration with cancer cells, etc

1 Leukemia, which is generally considered as a neoplastic infiltration of the bone marrow
2 Primary discrete and disseminated neoplasms of the bone marrow as multiple myeloma chloroma
3 Metastatic neoplasms as lymphoblastoma lymphosarcoma and carcinoma especially arising in the stomach, breast, prostate thyroid and hypernephroma

intestinal tract also is of importance but it is exceeded in frequency by the abnormal loss of blood from the uterus

The anemia which is a close second in incidence to the iron deficiency type is that in association with chronic infection The infection is found most commonly to be in the urinary tract the pelvis in women osteomyelitis and chronic pulmonary (non tuberculous) infections The incidence of additional types of anemia such as those due to nephritis true pernicious anemia and others will be discussed under the various sections dealing with these conditions

SIMPLE CHRONIC ANEMIA

Introduction

This type of anemia may be defined as a non hemolytic normocytic normochromic anemia due to multiple causes of which the most important is chronic infection Usually it is mild in degree and is not characterized by radical variations from the normal blood picture The condition generally is chronic and ordinarily is not amenable to any treatment except the removal or control of the cause Such an anemia is found in association with various chronic infections renal insufficiency cancer dysentery endocrine disorders such as hypothyroidism and Addison s disease and others and possibly vitamin deficiencies The first 3 causes named account for 95 per cent of all the cases

Incidence

This is one of the types of anemia encountered most commonly as demonstrated by observations at the University of Michigan Hospital As previously stated in a recent study[1] it was found that 12 5 per cent of all admissions to the hospital had an anemia of clinical significance and of these 39 per cent were of this simple chronic variety In a majority of these the anemia was relatively mild as the hemoglobin did not fall below 12 3 grams per 100 c c (79 per cent) in males and 11 1 grams per 100 c c (71 per cent) in females The red blood cell count in such patients varied between 3 and 4 0 millions per cubic millimeter

Simple Chronic Anemia Associated with Infection

The Cause of Anemia in Infection

Infection may produce an anemia by 2 wholly different mechanisms one an increased destruction of blood as seen occasionally in the septicemias and the other which is far more common is associated with a depression of the bone

Macrocytic anemias may be divided into two main types First the pernicious anemia group, which is the most important, because they respond to antipernicious anemia medication In this division are included true Addisonian pernicious anemia, sprue anemia associated with total gastrectomy, intestinal stenosis, and anastomosis, deficiency of the "extrinsic factor" and the macrocytic anemia of pregnancy In such anemias the mean corpuscular volume is usually 110 cubic microns and may reach a measurement of 140 to 150 cubic microns A second group is less well defined and does not respond to liver therapy Included in this division are the space occupying types, myelophthisic anemia, such as are seen in lymphoblastoma and leukemia and following acute hemorrhage In such anemias the mean corpuscular volume rarely is greater than 98 to 102 cubic microns, and the response to liver therapy is nil

Normocytic Anemia —Included in the normocytic anemias are aplastic anemia, the hemolytic anemias, the physiological anemia of pregnancy anemia of nephritis and most important of all from the standpoint of frequency, the anemia secondary to chronic infection Also in this group may be included at times the anemia due to displacement of the normal marrow by leukemia and other malignant processes Anemias of this type are not amenable to iron or liver therapy as a rule

Frequency of Various Types of Anemia

Some idea of the frequency of the various types of anemia may be gained from a consideration of a routine study made of the blood of all patients over 14 years of age who were admitted to the University Hospital of the University of Michigan in Ann Arbor during the year 1942 as in patients and out patients It was found that 12 4 per cent had an anemia This percentage was based on the assumption that the lower limit of normal of hemoglobin for males is 84 per cent (13 1 grams per 100 c c of blood) and for females 78 per cent (12 2 grams of hemoglobin per 100 c c of blood) In addition to determining the hemoglobin content in each patient the mean corpuscular hemoglobin concentration also was estimated in each case Consequently it was possible to determine if the anemia was normochromic or hypochromic in type The latter, which occurred in 41 per cent of those patients with an anemia in practically all instances was undoubtedly of the iron deficiency type In 39 per cent the anemia was of the normochromic variety, which most certainly was due in most instances to some type of chronic infection

It may be concluded therefore that in this part of the United States the most common type of anemia is due to an iron deficiency which experience has shown is secondary to chronic hemorrhage in a large majority of instances In males this arises most commonly from the gastrointestinal tract either as cancer or ulcer of the stomach cancer of the colon esophageal varices due to cirrhosis of the liver, chronic ulcerative colitis and hemorrhoids In females bleeding from the gastro-

nificance but inactive foci about the teeth apparently play no rôle in relation to an anemia of this type

Symptoms and Physical Signs

The symptoms and signs associated with such an anemia are slight if any The degree of anemia often is so mild that the clinician sometimes attributes the slightly lower hemoglobin percentage and red blood cell count reduction to a technical error and dismisses it as unimportant Rarely is such an anemia so severe as to cause dyspnea palpitation or pallor In my opinion however in combination with other factors such as toxemia very definitely it contributes materially to fatigue and an impaired sense of well being in many patients Furthermore, it undoubtedly prolongs the period of convalescence

Changes in the Blood

An anemia of this type usually is very mild the red blood cell count most commonly being between 3 5 and 4 0 million per cubic millimeter and the hemoglobin between 79 and 84 per cent in males and between 71 and 77 per cent in females It is almost always of the normochromic and normocytic type with a high color index a mean corpuscular volume between 86 and 96 cubic microns and a mean corpuscular hemoglobin concentration between 30 and 33 per cent Observation of the stained blood film rarely shows changes of importance in the erythrocytes although when the anemia is severe there may be slight anisocytosis, poikilocytosis is rarely if ever present The reticulocytes usually are in a percentage of 1.0 or lower An increase in the leukocyte count is observed infrequently, and when present it is usually due to an acute exacerbation of a chronic infection There are no important changes in the blood platelets

In some patients especially those with subacute bacterial endocarditis and acute rheumatic fever, a severe grade of anemia may develop In these diseases I have seen the red blood cell count fall below 2 0 million per cubic millimeter with a proportionate drop in the hemoglobin percentage

BLOOD CHANGES IN CANCER

In my experience an anemia of clinical significance develops in about three-fourths of all cases of cancer at some time during the course of the disease It is to be expected that such a complication is to be observed most frequently in the more advanced stages but occasionally it may be the presenting symptom which occurs as a relatively early manifestation In a study of 100 cases of malignancy Morrison[4] found that the red blood cell count was slightly decreased in two-thirds of the cases markedly reduced in one-eighth and normal or increased in one fifth

marrow and a decrease in blood production A simple chronic anemia due to the latter cause probably is the most frequent one encountered in clinical medicine, although the anemia due to it is usually mild or moderate in degree

Experimental work on animals has led Robscheit Robbins and Whipple[2] to conclude that diminished formation of hemoglobin in animals with infection or in whom a sterile abscess has been produced is due to a disturbance in the internal metabolism related to hemoglobin formation It is probable that the same mechanism is of importance in humans Faulty red blood cell formation is considered by Vaughan and Saifi[3] as a likely explanation of this variety of anemia They emphasize that in patients dying of a long continued infection it is not possible to demonstrate bone marrow aplasia or to find evidences of increased blood destruction as an explanation of the anemia It is their belief that in such patients there is some abnormality of hemoglobin synthesis, which depends on the presence of infection and that this accounts for the anemia Willison[4] is of the opinion from experimental studies on rabbits with tetanus and diphtheria toxins and with streptococcus and staphylococcus hemotoxins that these substances act on the bone marrow to produce an inhibition of maturation with a consequent failure of delivery of an adequate number of erythrocytes to the peripheral blood

Ample demonstration of the inhibiting effect of infection on the rate of red blood cell production is observed frequently in clinical medicine when patients with pernicious anemia are being treated with potent therapy, or when iron is given to patients with an iron deficiency anemia In either case an infection of any extent invariably will lessen markedly the anticipated response to either one of these effective remedies Regardless of the amount of medication which is administered to such patients it is not possible in a great majority of instances to bring the blood to normal until the infection is controlled

The most common type of infection which is associated with this variety of anemia, is the mild chronic type which continues over a long period of time Among the ones encountered most frequently are those involving the urinary tract and the pelvis, rheumatoid arthritis and chronic pulmonary infections such as bronchiectasis or lung abscess A very mild anemia may be observed in long continued pulmonary tuberculosis but this is often so slight as to be disregarded severe anemias in this disease are not common in my experience unless there have been repeated hemoptyses In about three fourths of the patients with subacute bacterial endocarditis due to the streptococcus viridans infection whom I have seen, there has been a moderate anemia of this type and in the remainder it has been more severe In chronic brucellosis such an anemia is observed sometimes[5] Many other forms of chronic infection may be responsible for an anemia of this nature, but in my experience focal infection has not been of great importance Occasionally in a growing child a chronic infection of the sinuses may be of si-

(7) Occasionally as mentioned in the section on pernicious anemia the intrinsic factor may be partially or entirely destroyed by an extensive infiltration of the stomach wall This has been observed to occur in linitis plastica and by this mechanism produce the blood picture of a macrocytic anemia resembling pernicious anemia closely

Type of Blood Picture in Cancer

In most instances when an anemia is present in a patient with cancer the blood picture is that of a hypochromic microcytic anemia due to chronic hemorrhage In the anemia due to bone marrow metastases the toxic effects of malignant growths and fever the findings are those of a normochromic normocytic anemia In the exceedingly rare instances of extensive malignant infiltration of the stomach especially of the fundic portion the anemia may be macrocytic in nature with a color index of 1 0 or greater and a mean corpuscular hemoglobin concentration of 30 to 33 per cent

In addition to changes in the erythrocytes there may be various other alterations in the blood of patients with malignant disease In my experience a leukocytosis usually ranging from 1 000 to 20 000 per cubic millimeter with an increase in the neutrophils of 75 to 85 per cent or more is not uncommon in patients with cancer According to Morrison[6] a leukocytosis occurs in about two-thirds of the cases

Hence it is well to keep in mind that a persistent and unexplained leukocytosis may be due to an obscure malignancy a fact of diagnostic importance which sometimes is overlooked The statement is made also by Morrison[6] that in over one half of the cases of leukopenia which he observed in patients with proven malignancy there were metastatic lesions This is a statement which I have not had an opportunity to confirm

Other observations made by Morrison in patients with proven malignancy are as follows The bleeding time rarely is prolonged and usually is less than one minute The coagulation time is within normal limits The blood platelets are either normal or increased The thrombocytosis according to Morrison is the basis for the non malignant thrombosis seen in patients with malignancy The tourniquet test rarely is positive The fragility test as determined with varying strengths of sodium chloride solutions rarely shows abnormalities

The average color indices associated with malignant lesions in various body organs were as follows colon 0 57 stomach 0 61 lungs 0 75 breast 0 76 pancreas 0 72 It was found by Baradulin[7] that in 81 cases of malignancy only one patient had a color index greater than 1 0 and in 3 patients there was a color index of 1 0

An anemia, therefore slight to marked, according to these figures was present in 80 per cent of the patients

Causes of Anemia in Cancer

The causes of anemia in patients with neoplastic disease, a number of which may be operative simultaneously, are as follows

(1) Acute or chronic hemorrhage Undoubtedly this is the most common cause for anemia in cancer and furthermore it is responsible for the most severe types The bleeding almost always occurs from some location in the gastrointestinal tract or from the uterus Rarely is bleeding from elsewhere in the body responsible for the anemia of a malignancy

(2) Anorexia A low food intake may be a contributing cause to this type of anemia by being responsible for a decrease in the intake of the extrinsic factor which usually means a limitation of meat eggs and milk in the diet Or there may be a suboptimal consumption of dietary iron and this in association with bleeding and infection may account for an anemia of the hypochromic type

(3) Bone marrow metastases In malignancy such as carcinoma of the stomach, prostate or breast for example, while there may be widespread metastases to the bone marrow which may account for an anemia, it is not a very common or important cause This is because, despite extensive bone marrow metastases there still remains a sufficient amount of uninvolved marrow to produce a normal number of erythrocytes

(4) The presence of fever which is observed often in all types of malignancy may act to inhibit the rate of formation of erythrocytes This is based on the assumption that the toxic products, which are responsible for the increase in body temperature act in a way similar to the toxins of bacteria and hence slow the rate of maturation of the red blood cells While this is probably true it cannot be said that substantial proof in support of such a statement is available at the present time

(5) Hypochlorhydria or achlorhydria may be present in a patient with malignancy and thereby impair the absorption of iron from the gastrointestinal tract The diminution or absence of free" hydrochloric acid may be due to the cancer itself as in neoplasm of the stomach or the patient may by chance fall into one of the group of 5 per cent of the population at large in whom it is estimated that an achlorhydria is present

(6) The possibility that the malignant lesions may involve to a certain extent the gastrointestinal function of absorption by the production of stenosis of the intestine or colon or serve as the basis for a diarrhea with rapid passage through the bowels thereby hindering absorption must be taken into consideration This undoubtedly does occur occasionally but probably it is a rare cause of anemia

orpuscular volume averaged 88 cubic microns the mean corpuscular hemoglobin 28 micromicrograms and the mean corpuscular hemoglobin concentration 31 per cent It may be said therefore that the average patient with nitrogen retention has a normocytic normochromic anemia of moderate extent In a few patients the mean corpuscular hemoglobin concentration may be below 30 per cent which would indicate a hypochromic type of anemia Usually there is little anisocytosis or poikilocytosis and it is rare to observe immature red blood cells in the circulating blood

The white blood cell count was found to be slightly elevated according to Parsons and Ekola Strolberg[11] averaging 13 839 per cubic millimeter but Brown and Roth[1] found an average of only 9 020 per cubic millimeter In uncomplicated nephritis with an anemia there is little or no shift to the left of the neutrophils but with an infection such as a sinusitis tonsillitis or otitis media there is commonly a leukocytosis with a shift to the left of the neutrophils

Although Brown and Roth[12] found a reduction in the number of blood platelets with counts which averaged 152 000 per cubic millimeter this has not been the experience of other observers Parsons and Ekola Strolberg[11] did not observe a material reduction in their cases and this is in accord with my experience Any bleeding tendency with the production of purpura in patients with chronic glomerular nephritis usually is considered to be due to an increased permeability of the capillaries of the vascular system

Treatment

The anemia of nephritis is not amenable to treatment with iron liver stomach preparations or any other form of therapy known at the present time except blood transfusions In one patient with a moderately severe anemia and nitrogen retention and an acidosis I administered potassium bicarbonate in doses of 5 0 to 8 0 grams daily over a long period of time No other treatment was given and much to my surprise the anemia disappeared in about 6 months Such an occurrence is rare in my experience in the spontaneous course of the disease It is a therapeutic observation which I intend to pursue further but about which I can say nothing additional at present

It is recognized that the severity of the anemia varies directly with the degree and duration of the nitrogen retention and at present we have no effective way of dealing with this condition Repeated blood transfusions may be tried[13] and some have reported that they have benefited the patients but in my experience they have not been of value From a prognostic standpoint it can be said accurately that as the anemia is almost without exception associated with nitrogen retention and hence renal insufficiency it always is a sign of grave importance and portends an ominous outlook

Anemia Due to Impaired Renal Function

Etiology

It has long been known that an anemia is commonly present in patients with chronic nephritis although its cause is obscure The suggestions have been made that it results from retained toxins[8], to an increased water content of the blood[9] and to the hematuria, but none of these possible causes are now accepted It appears to be clear that (1) the anemia cannot be attributed to blood loss ( ) that it does not result from aplasia of the bone marrow, (3) that there is no excessive blood destruction The general opinion which is not supported by substantial proof, is that the anemia develops as a result of diminished blood production although it has not been demonstrated that an aplasia of the bone marrow exists as a basis for this belief (4) it is generally accepted that the degree of the anemia is directly proportional to the severity and duration of the nephritis (5) all observers who have studied the problem are in agreement with the statement that the anemia is related to the inability of the body to eliminate nitrogen or at least they are in accord with the observation that, when an anemia of this nature is present there is almost always nitrogen retention in the blood stream This may be due to chronic nephritis, polycystic kidneys chronic prostatic obstruction or to functional failure of the remaining kidney when the other has been removed

The studies of Townsend Massie and Lyons[10] confirm the opinion that the anemia is in proportion to the degree of nitrogen retention They state that as a result of the retention of the end products of protein metabolism an acidosis develops as indicated by a decrease in the carbon dioxide combining power of the blood plasma According to these observers, when this reaches 30 volumes per cent there is a complete histamine refractory anacidity They interpret the findings to mean that there is improper absorption of food and iron Consequently there is a deficiency of "building material for sufficient red blood cell formation and production In my opinion there is a possibility that the long continued acidosis may be responsible for the anemia although the exact mode in which it operates if this is the cause, is obscure

Changes in the Blood in Nephritis

It is stated by Parsons and Ekola Strolberg[11] that there is a definite anemia in all patients with nephritis and an azotemia This is indicated by a study of their patients which showed a red blood cell count averaging about 3 0 million per cubic millimeter and a hemoglobin between 50 and 55 per cent (7 25 to 9 0 grams) In the group observed by Townsend, Massie and Lyons[10] the mean

IRON DEFICIENCY ANEMIA

Definition and Introduction

A commonly encountered hypochromic microcytic anemia which results from an inadequate supply of available iron in the body for the formation of the normal amount of hemoglobin Such a deficiency most commonly arises from chronic hemorrhage which occurs with greatest frequency from the gastrointestinal tract in males and the uterus in females Other causes of a subnormal amount of iron in the body are a low dietary intake malabsorption from the gastrointestinal tract and an increased demand for the metal which occurs during pregnancy and periods of rapid growth Furthermore any form of infection which may inhibit the proper utilization of iron may be responsible for such an anemia Regardless of the cause of the deficiency a gratifying response usually follows the therapeutic administration of iron in the proper doses

It is now recognized that the nutritional anemia of infancy and childhood chlorosis or the hypochromic anemia of adolescent girls the hypochromic anemia of pregnancy and of chronic blood loss and the idiopathic hypochromic anemia of adult women are all varieties of the same condition which results from a deficiency of available iron in the body These clinical syndromes have much in common They differ chiefly only because of the age and sex affected

History

Iron was introduced therapeutically by the Greeks as the result of the simple association of the idea that iron meant strength and protection and hence they argued it would undoubtedly be of value in the treatment of persons who suffered from weakness regardless of the cause The use of the metal in medicine is linked closely with the disease chlorosis because it was in this condition that prompt and dramatic results were first achieved by its use Although there may have been some vague reference to chlorosis by Hippocrates and other contemporary writers credit for the first description of the disease must be given to Johannes Lange (1485–1565) in the Epistola XX entitled De Morbo Virgineo found in his Medicinalium epistolarum miscellanea[1]

The name chlorosis was given to the disease by Jean Varandal in 1620[2] It is derived from the Greek word meaning green and the name green sickness was used commonly by Syndenham and other contemporary writers Thomas Sydenham[3] (1624–1689) the great English clinician must be accorded the credit for having popularized the use of iron with which he undoubtedly obtained good therapeutic results although he had no scientific basis for administering it In

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whom the lower limit of normal for hemoglobin in the circulating blood of adult males was set at 84 per cent (13 1 grams per 100 c c of blood) and for adult females 78 per cent (12 2 grams per 100 c c of blood) Levels below these arbitrarily set limits were regarded as representing anemias which were clinically significant Of the group having an anemia it was found that 41 per cent were of the iron deficiency variety and of these 16 8 per cent were mild and 24 2 per cent were moderate or severe in degree

As a further indication of the great incidence of this type of anemia the figures of Davidson Fullerton and Campbell[1] are informative They examined the blood of 3 500 persons representing the poor of Aberdeen Scotland and found an iron deficiency anemia to be present in 41 per cent of the infants under the age of 2 years in 32 per cent of the children of preschool age in 16 per cent of adolescent girls and in 45 per cent of adult women Mackay and associates[**] report that two-thirds of the women of the hospital class of London have such an anemia Hemoglobin levels below normal were found in approximately 40 per cent of college girls by Pryor and Ferguson[3] in 38 per cent of private patients by Bunce and his associates[24] and in about one fourth of the girls entering nursing training and 16 per cent of the women admitted to the wards of the Boston City Hospital by Heath[25]

Iron Metabolism in Relation to Hypochromic Anemia

The fundamental difficulty in an iron deficiency anemia is the inability of the body to synthesize hemoglobin due to the lack of available iron Hence the most important change in the blood is a reduction in the amount of circulating hemoglobin rather than a decrease in the number of red blood cells Consequently the blood changes are characterized by a low color index and a mean corpuscular hemoglobin concentration below 30 per cent and sometimes as low as 25 per cent

It is known that hemoglobin is composed of a protein of the histone class called globin and an iron containing pigment portion or protoporphyrin containing 0 335 per cent iron Apparently it is not often if ever that the body is deficient in any of the material essential for the synthesis of hemoglobin except iron There is therefore an important and constant need for this metal which must be supplied either from that which is ingested in the diet or from the amount stored as reserves in the body If the requirements are not met then each erythrocyte will contain less hemoglobin than normal and a hypochromic anemia will result

The Metabolism of Iron — Dietary iron in its ferric form is taken into the body in amounts between 12 and 16 milligrams daily by the average person in this country Two important actions which occur in the stomach are due essentially to the presence of the free hydrochloric acid in the gastric secretions These are

1731 Francis Hoffman[4] first gave an accurate and complete description of chlorosis, and in 1832 Ashwell[5] published a paper of 50 pages dealing with the condition and advocating the administration of iron in the form of ferrous carbonate and iodide in large doses

The development of our knowledge concerning the actual changes in the blood in chlorosis came slowly as methods of microscopic examination were introduced Thomas Willis made the observation that the blood in this condition was 'watery'[6] Lemery and Geoffry in 1713[7] demonstrated iron in the ash of the blood and in 1832 Fodisch[8] discovered that the blood of patients with chlorosis was deficient in the material It was observed by Popp[9] in 1845 that the color of the individual corpuscles was paler than normal which was confirmed by Duncan[10] who made the additional accurate observation that although the corpuscles were paler, they were not reduced in number It was not until the comprehensive studies of Hayem[11] on the blood that the disease was placed on a firm foundation in 1889 Pierre Blaud[12] in 1832 introduced his famous pills and by so doing laid down two important principles as follows, that the ferrous salts are more readily absorbed, and that large doses of iron are necessary to obtain the optimum effects

The eclipse of iron therapy was inaugurated by Bunge and Abderhalden[13] in 1898 who laid the basis for the belief that small doses only of iron were necessary and thereby impeded rational iron therapy for at least a quarter of a century In 1922 Lindberg[14] readvocated the administration of large doses of iron and this was endorsed by Meulengracht[15] shortly thereafter

Idiopathic hypochromic anemia of middle aged women was described first by Knud Faber in 1913[16] The syndrome of a hypochromic anemia and dysphagia was described by Kelly[17] and by Paterson[18] in 1919 and by Vinson[19] in 19 2 It is generally known in this country as the Vinson Plummer syndrome

Etiology

Frequency

The iron deficiency anemias undoubtedly are the most important ones in medicine because they are encountered so commonly, and also because gratifying results are obtainable by the proper use of iron a relatively cheap form of medicine As previously stated some idea of the frequency of this type of anemia can be gained by the figures which were collected at the University of Michigan Hospital in Ann Arbor Michigan, during the years 1942 and 1943[20] In a routine study of the hemoglobin of all patients over 14 years of age admitted to the hospital and out patient departments it was found that 12 4 per cent had an anemia This percentage was based on a study of the blood of slightly over 11,000 patients in

in all of the tissues of the body where it performs an important function probably in relation to tissue metabolism This iron is not available however for the formation of hemoglobin

The Causes of Iron Deficiency — A deficiency of iron and hence an iron deficiency anemia may arise from (1) an insufficient dietary intake (2) chronic hemorrhage (3) an increased demand due to growth pregnancy and lactation (4) impaired absorption from the gastrointestinal tract (5) impaired utilization of iron due to infection Not infrequently more than one of these factors are operative in the same patient as a cause of this type of anemia It is my opinion however that of these causes only chronic hemorrhage is capable of producing an anemia when acting alone The others may contribute to its severity but two or more must be active before an anemia results

Hemorrhage as a Cause of Iron Deficiency Anemia — Chronic hemorrhage undoubtedly is the most frequent cause of iron deficiency anemia in adults in both males and females In males the bleeding usually is from the gastrointestinal tract due to hemorrhoids peptic ulcer or to carcinoma of the stomach Other important causes are esophageal varices chronic ulcerative colitis carcinoma of the cecum the sigmoid or the rectum In females bleeding from the gastrointestinal tract also is frequently the cause of anemia but it is surpassed in importance by uterine bleeding

The bleeding regardless of its source either in males or females commonly is in small unnoticed quantities of blood and consequently the patient often is unaware that there is a significant loss of blood This is especially true in excessive menstrual loss It has been found by Barer and Fowler[27] that the average menstrual flow in a normal woman is about 50 c c of blood at each period which means an iron loss of 19 7 milligrams They also observed what it has taken the medical profession a long time to learn that neither the duration of the period nor the number of napkins used are reliable criteria of the amount of blood lost although they do give some indication The loss of as much as 179 c c per period which was regarded as normal by one of their subjects would require a positive iron balance of 3 29 milligrams for each day of her 4 day cycle According to these observers this is more than is ordinarily stored and it could be gained only by the addition of iron to that obtained in the diet It should be emphasized that the loss of excessive quantities of menstrual blood frequently plays a rôle in the causation of iron deficiency anemia It should always be considered as a possible explanation of an anemia of this type in a female despite the statement that her periods are normal

It should be axiomatic that if an adult has an anemia with a color index of 0 6 or less and a correspondingly low mean corpuscular volume hemoglobin concentration in the vicinity of 25 per cent the possibility that it is due to chronic bleeding is great In the female as previously emphasized it may be associated

(1) rendering the metal soluble and ionizing it and (2) preventing the formation of insoluble iron compounds such as phosphates Having been acted upon in the stomach the iron then passes into the upper gastrointestinal tract, where by some unknown means it is reduced to the ferrous state and absorbed as such It is thought that iron leaves the intestines and enters the blood in this valency only

In recent years an important fact concerning the absorption of iron has been discovered by Hahn and his associates [6] These observers found that the intestinal mucosa has a specialized ability to absorb or reject iron, depending on the immediate requirements of the body for the metal Ordinarily the normal adult especially the male, has need for the absorption of only minimal amounts of iron as negligible quantities only are lost from the body Consequently although 12 to 16 milligrams are taken in the diet each day only a very minor fraction is absorbed, because usually the normal adult is well supplied with iron reserves On the other hand, if a hemorrhage should occur or the need for iron is created by some other reason then the intestinal mucosa functions automatically to absorb an increased amount of iron It can be said, therefore that a large part of the metal ingested by a normal person usually passes through the intestinal tract, instead of being absorbed and then excreted as some had previously thought

Furthermore it has been demonstrated that once iron enters the body it normally does not leave except in the menstrual flow, in the fetal tissues in the milk and in exceedingly small amounts in the bile and the urine In the male this means that practically no iron normally leaves the body When this is taken into account it is plausible to surmise that the injection of iron in the form of a large number of blood transfusions in the male might cause the accumulation of a large surplus of the metal in the tissues and the condition of hemochromatosis result Such a condition did develop in one of our patients at the Simpson Memorial Institute who had aplastic anemia and received 137 blood transfusions over a period of about 8 years It is calculated that during this time about 68 000 c c of blood was injected containing 36 3 grams of iron In the latter months of the patient s life his skin acquired the characteristic color of hemochromatosis he developed a glycosuria and a cardiac disturbance which were finally responsible for his death At necropsy there was a deposition of a large amount of iron in the skin the liver pancreas myocardium and various other tissues of the body This case is described in greater detail in the section dealing with Aplastic Anemia

Normally the total amount of iron in the body is estimated to average about 4 2 grams of which almost 80 per cent is found in the hemoglobin of the circulating blood where it is present in a concentration of 0 335 per cent There is a reserve iron supply of about 0 3 grams which is stored chiefly in the liver, spleen bone marrow and to a lesser extent in the other tissues of the body It is calculated that this quantity is sufficient to provide for the regeneration of between 600 and 800 c c of blood The remainder of the iron about 1 2 grams is found

greatest growth and during the period when menstruation is present and pregnancies occur there is a definite increase in the demand of the body for iron This is recognized now by all hematologists as true and these factors therefore are regarded as highly significant ones in the production of the hypochromic anemias

The increase in the iron requirements during the period of growth is attributed to two conditions namely (1) to the augmented total cellular content of the body and (2) to the increase in the blood volume As iron is known to be present in every cell of the body it is logical to conclude that with growth there must be some increase in the total body iron due to the added number of cells present A much more important need for iron however is created by the increase in the blood volume It has been estimated by Heath and Patek[23] that the average increase in the blood volume between the fourteenth and fifteenth years is 340 c c This when combined with the menstrual loss average about 650 c c in females during the course of one year would total 1 000 c c or one fourth of the total blood volume at that age This amount of blood must be formed which requires a certain amount of additional iron and in addition the other requirements of the body for this metal must be met While the iron necessary for the synthesis of this additional hemoglobin ordinarily is supplied by the normal average diet a hypochromic anemia is likely to appear at this time if the dietary intake is insufficient or if additional factors such as an achlorhydria a chronic infection or hemorrhage is present

One of the types of iron deficiency anemia most frequently encountered is observed in infants This results chiefly from the combination of rapid growth *and a diet consisting exclusively of milk which is known to be poor in iron* Other factors may contribute also to this variety of anemia and these will be discussed under the section dealing with the Iron Deficiency Anemia of Infants

Role of Pregnancy in Producing Iron Deficiency Anemia — An iron deficiency anemia commonly occurs in pregnancy and will be discussed in more detail in the section on the Anemias of Pregnancy It is obvious that an additional amount of iron is required during pregnancy in order to form the fetal tissues including the blood It should be kept in mind however that there is some conservation of iron during gestation as a result of the absence of about 10 menstrual periods Although there is not entire agreement concerning this it seems fair to state that the iron requirements of normal pregnancy including ordinary bleeding at the time of delivery does not exceed by two or three times the loss of blood by normal menstruation over a corresponding interval This would approximate the amount of blood provided by the average blood donor for transfusion purposes on one occasion that is approximately 500 c c If during pregnancy however there is in addition to this demand a deficiency of iron in the diet or an achlorhydria a hypochromic anemia of considerable extent may develop This is especially true if the pregnancies are repeated at frequent

with excessive loss of blood in what is considered to be "normal" menstrual periods whereas in the male it is likely to be from the gastrointestinal tract This may be established readily by testing the stools for occult blood subjecting the patient to gastrointestinal roentgen ray studies, including a barium enema and sigmoidostomy, and keeping in mind the fact that certain lesions in the stomach, intestines and colon may escape detection in the roentgen ray examination

Deficiency of Dietary Iron in Relation to Anemia — It is not common for a deficiency of dietary iron alone to result in an anemia of the hypochromic type although a curtailment of the intake may be an important contributing factor especially in women and children From a theoretical standpoint it is unlikely that an adult male could possibly partake of a diet which would be so low in iron as to be the sole cause of such an anemia Also it is not likely but possible in the female that additional factors such as menstruation pregnancy and lactation may combine with a low dietary intake to result in an iron deficiency anemia

If an average adult has an iron intake of about 12 milligrams and 50 per cent only of it is available then it may be estimated that 6 milligrams is utilized to replace that which is lost in the feces and urine and to create reserve stores It is probable, however that many persons in this country and throughout the world receive less daily iron than this For example if the daily intake were between 6 and 8 milligrams, the amount of available iron would then be between 3 and 4 milligrams on the assumed basis that only 50 per cent in the ingested food is utilizable This is probably adequate even in the case of menstruating women in whom, in addition to the loss of 1 milligram in the urine and feces it is reasonable to assume an additional average daily loss of a milligram in the menstrual flow This total average daily loss of 2 milligrams is replaced easily by an intake of 3 to 4 milligrams daily

These approximate estimates of the iron requirements emphasize two matters in relation to the etiology of the iron deficiency anemias as follows, (1) the clinical observation that a low iron diet is rarely, if ever, the sole cause of an iron deficiency anemia is substantiated and (2) when the dietary iron is reduced to a low level there remains only a small margin of safety If some other etiological factor then comes into play such as an infection or loss of blood or perhaps only the presence of an achlorhydria which impairs the absorption of the metal then a significant depletion of iron does occur in the body and a hypochromic anemia will develop

Increased Demand for Iron Due to Growth, Pregnancy and Lactation — It is generally agreed that the iron deficiency anemias are much more prevalent in infants children and adolescents during the period of growth and in women throughout the reproductive period of life This is because at the stages of

animals that have been rendered anemic by repeated bleeding one would expect to find a deficiency of stainable iron in the liver spleen skin and bone marrow provided iron therapy had not been given

Suzman[29] has reported the necropsy on a patient with Vinson Plummer syndrome who succumbed following esophagoscopy with rupture of the esophagus and subsequent infection The hemoglobin had been 30 per cent and the red blood cell count 3 5 millions per cubic millimeter just prior to death No gross pathological abnormalities were noted in the heart gastrointestinal tract spleen pancreas suprarenals kidneys or thyroid gland No mention was made of changes in the stomach The esophagus showed a fold of mucous membrane forming a mucosal band This was thought to account for the obstruction at the upper end of the esophagus and the complaint of dysphagia during life The mucosa and muscle of the tongue and esophagus showed definite histological abnormalities consisting chiefly of hyperkeratinization of the epithelium with areas of desquamation and of degenerative atrophic changes in the underlying muscle The possibility is mentioned that the hyperkeratinization of the epithelium may have been due to a deficiency of vitamin A

A case[30] has been reported in a 50-year-old woman who had been given iron for a period of 3 weeks before death and then died following an operation on the uterus for a myoma In this patient there was a widespread atrophy of the mucous membranes of the tongue the esophagus and stomach with hemorrhages in the mucosa of the latter viscus

Gastroscopy during life has been reported[31] as showing a pale gray, atrophic mucosa

The sternal marrow in patients with an iron deficiency which is described in detail under the appropriate section shows a normoblastic hyperplasia

General Clinical Manifestations of Iron Deficiency Anemia Regardless of the Cause of the Depletion of Iron

Symptoms and Signs

The complaints of patients with an iron deficiency anemia resemble those encountered in any form of anemia and are directly proportional in intensity to the degree of reduction of the hemoglobin of the circulating blood In general it may be said that they are ease of fatigue and weakness dyspnea palpitation pallor vertigo periods of faintness and dizziness anorexia and vague digestive disturbances In some instances the patients complain mainly of nervousness One young woman recently was referred to me with this as a chief complaint this had been thought to be due to a toxic goiter It was found however that there were no classical signs of thyrotoxicosis present and that the basal metabolic

intervals, if lactation is long continued and if the iron reserves of the body are depleted at the time pregnancy is established

Impaired Absorption of Iron — Impaired absorption of iron may contribute importantly to the production of an iron deficiency anemia and it may result from two different mechanisms In the rapid passage of the contents through the intestinal tract as in chronic diarrhea there may be a loss of iron because the time of passage is too short for the efficient absorption of the metal In one of my patients with chronic ulcerative colitis the bowel content when marked off with carmine, was observed to traverse the entire intestinal tract in 30 minutes The importance of this as a cause for an iron deficiency has not been determined accurately but theoretical considerations indicate that it cannot be disregarded

Of recognized importance is the presence of an achlorhydria as a cause for the impaired absorption of iron Apparently the efficiency of the absorption of iron from the gastrointestinal tract has a definite relationship to the hydrochloric acid content of the gastric juice If this is reduced or absent absorption of the metal always is less efficient An achlorhydria, therefore, would have the effect of converting a high iron diet into a low iron diet when considered from the standpoint of the delivery of iron to the body tissues

Although the organic acids provided by fermentation will replace to some extent the hydrochloric acid in rendering the food iron absorbable, their action is much less efficient It is not thought that impaired absorption alone can be a cause for a hypochromic anemia, but it may be an important contributing factor

Relation of Infection to Iron Deficiency Anemia — Undoubtedly there are other important contributing factors to the etiology of iron deficiency anemia in addition to those which have been discussed Clinical observation has indicated clearly that one of these is the presence of chronic infection There is no doubt that this will intensify such an anemia, and furthermore that it will inhibit the regeneration of hemoglobin to a certain extent, when treatment with iron which ordinarily is efficient is administered Such an action may be due to bacterial toxins which in some unknown manner may interfere with the synthesis of hemoglobin possibly iron excretion is accelerated by the increased breakdown of body cells what is more likely but probably minor in its effects, the appetite during an infection may be so impaired as to reduce the intake of dietary iron to a level below the necessary requirements

Pathology of the Iron Deficiency Anemias

Our knowledge of the pathological changes which are associated with an iron deficiency anemia per se, is incomplete as there have not been reported a sufficient number of necropsy studies on untreated patients Judging from the findings in

Koilonychia should be considered to be evidence of iron deficiency until otherwise proven because in almost all cases it is seen in association with an anemia of this type As women until the menopause require more iron than men it is to be expected that the condition will occur much more commonly in them It has been rare in my experience in males although I have observed it sometimes without an explanation Recently I examined a male age 47 years with moderately advanced rheumatoid arthritis who had a definite koilonychia for which I could find no cause The blood was normal in all respects there was no history or evidence of chronic bleeding nor was an achlorhydria present It has been claimed by some[33] that koilonychia can occur in the presence of a normal hemoglobin and red blood cell count but that in these cases there is a low serum iron

In my experience spoon nails tend to disappear in persons with hypochromic anemia when iron is administered and this is the conclusion of other observers A male age 46 reported by Clarke[34] had a hypochromic anemia associated with bleeding hemorrhoids and with this there was koilonychia which disappeared completely following treatment with iron on two occasions there having been 7 years between the two episodes

I have observed koilonychia only in adults and Faber and his associates[34] reported that the condition was not present in 10 infants 7 to 24 months of age with an iron deficiency anemia although in a few instances it has been said to have been present in early childhood and a family incidence has been reported[35 36 37]

Certainly the presence of koilonychia should direct attention toward the diagnosis of an iron deficiency anemia but the condition is reported as occurring in pernicious anemia thyroid diseases and even in polycythemia[8]

Laboratory Findings

Blood Examination

The characteristic findings in the blood of patients with an iron deficiency anemia are those of a microcytic hypochromic anemia There is uniformly a greater decrease in the hemoglobin of the erythrocytes than there is a reduction in the total red blood cell count For example a typical finding would be a red blood cell count of 3 5 million per cubic millimeter and a hemoglobin of 35 per cent (5 46 grams) which would give a color index of 0 5 With these there would be a mean corpuscular hemoglobin concentration of 25 to 26 per cent It is unusual to observe such a low color index and mean corpuscular hemoglobin concentration in any other anemia except in one due to an iron deficiency A similar change may occur occasionally however in other conditions for example

rate was normal An iron deficiency anemia was present, however, due to an excessive menstrual flow, with a hemoglobin of 50 per cent Another one of my patients entered the hospital on account of an acute respiratory infection and the hemoglobin was found to be 50 per cent on routine examination She had been working as a graduate nurse on 8 hours duty allegedly without difficulty On close questioning however, she admitted excessive fatigue but according to her statement she had "never felt any other way in her life and thought that it was a normal state of health" In most patients however, there are definite complaints, although usually they are not of such an extent as to prevent them from doing some housework or at least in a half hearted manner to attempt to carry on a normal existence

Physical examination usually reveals a definite degree of pallor in a person who may be undernourished or show no sign of emaciation Evidences of recent loss of weight usually are not conspicuous, and in some cases especially in the so-called idiopathic hypochromic anemia of middle aged women, there may be even moderate obesity There is almost always a hemic murmur at the apex and frequently at the base of the heart which is systolic in time The spleen and liver are rarely enlarged, and the lymph modes are not palpable In some patients there may be atrophy of the papillae of the dorsum of the tongue, resembling the condition seen in some patients with pernicious anemia

Koilonychia

Of special importance in iron deficiency states is the presence of a curious concavity of the finger nails designated koilonychia which is observed in 15 to 30 per cent of all patients with an iron deficiency state The term ' koilonychia which is derived from the Greek meaning "spoon nails denotes a condition characterized by a central, spoonlike concavity of the finger nails with flat lateral margins and a tendency to eversion of the end of the nail Any number of the nails may be affected but in my experience the thumb and forefingers have shown the most conspicuous changes I have never observed these alterations in the toe nails but this may be because often they are so misshapen from the wearing of shoes that it is difficult to determine whether mild degrees of koilonychia are present or absent

According to Clarke[37] associated changes in the nails which are observed commonly are flattening exaggerated longitudinal striations and increased thinness and brittleness In the opinion of this observer these changes may be present in patients with hypochromic anemia not displaying koilonychia I have observed flat nails called ' platonychia ', in persons with an iron deficiency anemia and consider that they are a less advanced stage of koilonychia with the same clinical significance as the latter

Gastric Analysis

Hypochlorhydria or achlorhydria is present frequently in patients with this type of anemia This statement requires some qualification however as the state of the gastric secretions is dependent to a certain extent on the cause of the iron deficiency For example this variety of anemia is common in patients with peptic ulcer due to chronic hemorrhage from the ulcerative area in the stomach or duodenum but free hydrochloric acid is present always in this condition often in excessive amounts On the other hand a histamine resistant achlorhydria is present almost always in the idiopathic hypochromic anemia of middle aged women A similar state of the gastric secretions may be observed occasionally in the hypochromic anemia of childhood In chlorosis the acidity of the gastric juice is said to be normal or decreased

There is also a reduction or absence of pepsin in severe cases of iron deficiency anemia but as one would expect the intrinsic factor of Castle has been demonstrated to be present[24]

Other Laboratory Findings

The serum bilirubin is normal or diminished as is the icterus index The plasma proteins may be reduced in long standing cases with a severe anemia Probably this is associated with a persistently low protein intake over a long period of time and is therefore only indirectly due to the anemia If questionable pitting edema is disregarded this physical finding has not been common in my experience The blood iron usually is reduced in proportion to the amount of hemoglobin

VARIOUS TYPES OF IRON DEFICIENCY ANEMIA

As has been stated previously the iron deficiency anemias may be of various types depending almost entirely on a difference of age and sex as a basis for the several syndromes The main features of the more important types will be discussed briefly in the following paragraphs

Hypochromic Anemia of Infancy and Childhood (Nutritional Alimentary Chlorotic Anemia of Infancy)

This is one of the most common types of iron deficiency anemia its frequency being due to the fact that there is a tendency for every infant to be in negative iron balance during the first 6 months of life This is attributed to an increased demand for iron associated with rapid growth and sometimes also a low iron intake due to a diet which may be composed almost exclusively of cow s milk which is known to be poor in this metal The requirements of increased blood

Cooley's anemia, which is not related primarily to a disturbance of iron metabolism

Another characteristic finding is the decrease in the size of the cells to below normal. This is shown by the measurement of the average diameter, which usually is 6.2 to 6.7 microns as compared to a normal average of about 7.2 to 7.5 microns. The diminution in the average size of the erythrocytes is shown in the reduced mean corpuscular volume, which usually is between 60 and 80 microns, as compared to a lower limit of normal of 86 cubic microns. The Price Jones measurements show a peak to the left of the normal of 7.5 microns, which means that the greatest percentage of erythrocytes have a diameter of less than 7.5 microns. The mean corpuscular hemoglobin usually is between the limits of 15 and 21 micromicrograms.

Examination of a stained blood film from such patients reveals the presence of small red blood cells which contain a reduced amount of hemoglobin. When the hemoglobin is greatly diminished, the erythrocytes may appear as nothing more than rings of hemoglobin, the clear non staining central area occupying a considerable part of the cell. Unless the anemia is severe, the red blood cells are of fairly normal shape and the variation in size is not great. In untreated cases the reticulocytes usually are between 1 and 2 per cent, and there is rarely evidence of active regeneration of the red blood cells as indicated by the presence of nucleated erythrocytes or diffuse and punctate basophilia. Following the administration of iron there is characteristically an increase in the percentage of reticulocytes on about the fourth or fifth day of treatment, but this is much less than is seen in patients with pernicious anemia who have received potent anti pernicious anemia treatment, as the peak in the former is rarely greater than 8 to 10 per cent.

The leukocytes show no constant change, as the white blood cell count usually is within normal limits, but in some chronic cases it may be below 4 000 per cubic millimeter. If there has been a fresh hemorrhage of any great extent, a slight leukocytosis with an increase in the percentage of the neutrophils commonly is present. The blood platelets ordinarily are normal in number, but also in case of an acute hemorrhage they are likely to be increased for short intervals of time after the hemorrhage.

Bone Marrow

The bone marrow is characteristically hyperplastic with a predominance of normoblasts. In contrast to the bone marrow of patients with pernicious anemia in relapse megaloblasts are lacking, although young normoblasts may be noted. There is no important variation from normal in granulopoiesis. The normoblastic proliferation disappears following specific medication with iron.

Changes in the Blood — The typical changes are those of a hypochromic anemia In the 63 cases reported by Thayer[39] the red blood cell count averaged 4 1 million per cubic millimeter and the hemoglobin 42 per cent The cases observed by Cabot[40] most frequently had a red blood cell count in the vicinity of 3 5 to 4 0 million per cubic millimeter with a hemoglobin between 50 and 60 per cent It has been found by Heath and Patek[25] in the routine examination of 38 presumably healthy student nurses in Boston between the ages of 18 and 23 years that 26 per cent had a moderate anemia with a hemoglobin between 70 and 79 per cent They state also that a hypochromic anemia of severe grade and one responding to iron is observed fairly frequently in adolescent girls who enter the Boston City Hospital for the treatment of some other disease such as pulmonary tuberculosis pleurisy with effusion lobar pneumonia and pyelitis This corresponds with our experience at the University Hospital in Ann Arbor both with respect to the student nurses and adolescent girls admitted to the hospital for one reason or another

Treatment of Chlorosis — It was in this condition mainly that iron received its well deserved reputation during the past three centuries It should be administered as ferrous sulphate in doses of 0 3 gram (5 grains) three times daily after meals and the patient observed for recurrences It is likely that this form of medication will be necessary until full growth is attained and even then there may be a tendency to relapse In a few patients in my experience there has been a hypermenorrhea which apparently has prevented the proper response to the medicament When this occurs one should suspect the possibility of hypothyroidism and if the basal metabolic rate is significantly lowered and the blood cholesterol elevated a cautious trial of desiccated thyroid gland is worth while for in some instances it may control the excessive loss of blood

Chronic Hypochromic Anemia

Synonyms — Idiopathic hypochromic anemia simple achylic anemia chronic microcytic anemia essential hypochromic anemia

Definition — A chronic microcytic hypochromic anemia almost always occurring in women between the ages of o and 50 years who have either an achlorhydria or a reduction in the amount of hydrochloric acid in the gastric secretions The condition is due to a lack of available iron in the body resulting from diverse causes the most important being chronic hemorrhage and impaired absorption of iron It responds uniformly and favorably to iron

Etiology — This syndrome occurs almost entirely in females This is because the iron requirements are greater in females to the time of the menopause and because excessive bleeding is more common in this sex as a result of excessive menstrual flow The anemia develops largely on account of the chronic hemor

formation must be met in such cases from the reserves of iron, which have been stored mainly during the last trimester of pregnancy and by the high rate of conservation of iron from hemoglobin destruction during the initial 2 weeks of life Other contributing factors are a maternal iron deficiency, which may mean that the infant is born with a normal hemoglobin of the circulating blood but with inadequate iron reserves prematurity of the infant, low birth weight or multiple births, all of which result in a deficient prenatal storage also an added demand associated with a rapid growth rate during the first year of life Various additional etiological factors of importance are anorexia, achlorhydria and diarrhea which interfere with the absorption and utilization of iron

Chlorosis

This variety of hypochromic anemia may be defined briefly as an iron deficiency anemia occurring in adolescent girls

Incidence — A curious and fascinating history is associated with this condition There can be no doubt that this type of anemia did exist fairly commonly in the past as evidenced by careful hematological examinations While I cannot speak for the clinicians of the seventeenth century and later who emphasized the high diagnostic value of the green tint of the skin from which the disease derived its name I can say that such a color does not exist today in adolescent girls who have had a long standing and severe iron deficiency anemia Even Richard Cabot in the 1915 edition of Osler and McCrae s System of Medicine expressed a most conservative attitude in respect to this He says 'It takes the eye of faith to see any justification for the title of the disease" and further along in his article is his statement If one exercises a great deal of imagination one might possibly see the slightest imaginable tint of olive green in the shadow beneath the chin, but that is all In this same article written in 1915 Cabot concludes that the condition is disappearing at least in the United States There has been a distinct tendency to regard this type of anemia as a mysterious syndrome which existed only in the past This however is not entirely true If one does not pay too much attention to the significance of the name as indicating an important sign, it may be said that at least a mild chlorosis, as defined in the first sentence of this section is not a rare disease in this country at present

Etiology — In girls of the adolescent age it is easy to understand why an iron deficiency might develop commonly This is because there is an increased demand for iron associated with the rapid growth at that age and in addition with the onset of menstruation there is an added factor of blood loss which may be excessive If the patient should have anorexia or partake of a diet which is poor in iron or develop an infection or have an achlorhydria, there would be added causes for the iron deficiency

number of patients tumors of the uterus may be the basis for the chronic loss of blood

Blood Examination —The blood shows the typical changes observed in a hypochromic microcytic anemia In the group of patients studied by Wintrobe[a] 90 per cent had a red blood cell count between 3 000 000 and 5 150 000 per cubic millimeter and in 74 per cent the hemoglobin was 6 to 10 grams (38 to 64 per cent on the basis that 15 6 grams equal 100 per cent)

Gastric Analysis —An achlorhydria is present in about three fourths of these patients and in the remainder there is a hypochlorhydria In those patients with an achlorhydria it usually persists despite the fact that the anemia disappears with iron therapy There is some reason to believe that in some patients it has been present since birth Perhaps one reason why such persons have a tendency to relapse is that the achlorhydria remains and therefore there is constantly a subnormal absorption of iron

Vinson Plummer Syndrome

The association of dysphagia superficial glossitis and a hypochromic anemias which responds to iron therapy has been regarded as a clinical entity and is designated in this country as the Vinson Plummer syndrome The condition was reported in 1922 by Vinson[19] under the title of Hysterical Dysphagia but according to Suzman[9] the disorder had been described previously by Kelly[17] and by Paterson[15] in 1919 in England Except for the dysphagia and certain psychic symptoms all of the clinical manifestations are entirely similar to those of idiopathic hypochromic anemia

The etiology of the dysphagia is in dispute The current theories regarding its cause are (1) that it is a hysterical manifestation (2) that it is a spasm or failure of the pharyngeal-esophageal sphincter to relax resulting from an inflammatory involvement of the nerve supply in the pharyngeal-esophageal region or involvement of Auerbach s plexus (3) that webs band or raised folds of mucous membrane are the definite cause of the obstruction (4) that it is associated with a condition of hyperkeratinization of the epithelium of the tongue hypothorax and esophagus with areas of desquamation and atrophic degeneration of the underlying muscles The arguments for and against these views and a summary of the literature are given by Suzman[9]

It seems as though the etiology of the anemia is related to those factors recognized as causative in idiopathic hypochromic anemia especially a low intake of iron in the diet and probably impaired absorption associated with a low gastric acidity The cause of the dysphagia must remain a matter of conjecture until additional information is obtained regarding it

Treatment —The treatment of the condition may be divided into four

rhage and an impaired absorption of iron as a result of the commonly associated achlorhydria or decrease in the amount of hydrochloric acid in the gastric secretions Other contributing factors are a dietary intake which is deficient in iron and frequent pregnancies at relatively short intervals

Symptoms and Signs — The onset is insidious, and commonly the patient has complained of poor health for many years Often the statement is made that "I have never been in good health all of my life" In some instances this is probably literally true for it is known that an iron deficiency may exist practically from birth Hence the patient may have had consecutively with varying degrees of intensity the hypochromic anemia of infancy, the chlorotic syndrome of adolescence the hypochromic anemia of pregnancy and chronic hypochromic anemia of middle age It is some consolation to know that usually a patient's troubles are over from this standpoint with the completion of the menopause Just prior to this event however there is likely to be an excessive loss of menstrual blood and an accentuation of an already existing anemia

In some patients although an anemia of moderate extent has been present for a long period of time there seems to have been a minimum amount of incapacitation, for apparently there may be an adjustment of the body in some unknown manner to the low hemoglobin levels

The symptoms usually are those associated with any type of anemia of which asthenia and ease of fatigue predominate Other complaints are vague upper abdominal distress the eructation of an excessive amount of gas, the passage of soft mushy stools, low resistance to respiratory infections emotional instability and vague aches and pains Menorrhagia is common, as on careful questioning it will be discovered that about three fourths of these patients may have an excessive loss of menstrual blood A certain amount of glossitis and atrophy of the papillae of the tongue occurs in about one third of these women but rarely do such changes attain the prominence observed in patients with pernicious anemia Numbness and tingling of the hands and feet may be present also but it differs from that observed in patients with pernicious anemia, as only 15 to o per cent have this complaint and it is milder and less persistent

Physical examination shows a variable degree of pallor without evidence of a yellowish tint, usually fair nutrition or occasionally even moderate obesity and frequently, oral sepsis, which probably has no etiological relationship to th disease In some patients there is an acute glossitis which manifests itself as an abnormal redness of the tip or the entire tongue or atrophy of the papillae The edge of the liver and the spleen may be palpable in a few patients, but these organs never are grossly enlarged Occasionally there is slight pitting edema but if this is pronounced some other explanation than the anemia should be sought Th heart often is borderline in size and a soft apical systolic murmur is present commonly Pelvic examination should never be omitted as in an appreciable

given parenterally in adequate doses alarming and sometimes dangerous reactions will result If the recommended dose of iron is given intramuscularly or intra venously and no untoward reactions follow, then it can be concluded that the quantity of iron administered probably has been inadequate from a therapeutic standpoint *Furthermore I have never found anything which can be added to iron which will enhance its value to the patient* Usually if iron is given in full doses there is a definite increase in the hemoglobin by the eighth to the tenth day and this continues at the rate of about 1 per cent daily until a normal level is reached Never in my experience have I been able to find anything including copper ventriculin liver the vitamins or any other substance recommended especially by the manufacturing pharmacists which will cause the hemoglobin to increase at a more rapid rate

The preparation of iron which I recommend above all others is ferrous sul phate given in enteric coated pills in doses of 0 3 gram 3 times daily after meals or if the desired result is not attained within 2 weeks then the dose should be increased to 0 6 grams 3 times daily following meals I am aware that in giving the iron in enteric coated pills the action of the gastric juice which probably is desirable but not essential may be eliminated and hence theoretically at least this may seem to be an unwise practice It should be remembered that in many cases however there is an achlorhydria and furthermore the observation of the effects of such a preparation in enteric coated pills has demonstrated many times to me that it is highly effective There is no serious objection however if one desires to giving the material in ordinary capsules or tablets which are not enteric coated Although others have claimed that such medication may be followed by nausea or anorexia or in some cases by diarrhea these complaints have occurred uncommonly in my experience Never have I been obliged to discon tinue iron medication on account of such symptoms

There is abundant evidence in man to prove that the ferrous salts divalent are superior to the ferric form in the treatment of these anemias It has been found by Moore and his associates[4] in their studies utilizing radioactive iron that in human subjects the ferrous iron appeared in the circulating erythrocytes in a shorter time than the ferric iron There appears to be therefore a sound reason for the preference of the divalent form of the metal in the treatment of the iron deficiencies of man

For infants and young children the following stable elixir may be employed

Dilute hypophosphorous acid	0 6 c c
Ferrous sulphate	3 0 grams
Dextrose	30 0 grams
Chloroform water to	120 0 c c.

Sig 4 c c three times daily after meals

parts, namely, (1) the passage of esophageal bougies to relieve the dysphagia, (2) the administration of iron in full doses as described under the section on treatment at the end of the chapter, (3) prescribing a full diet and the treatment of the associated vitamin deficiencies (4) investigating and treating the psychic disorders, which are commonly present, and reassurance of the patient

Although the immediate effect of therapy is gratifying there is always a tendency for these patients to relapse Hence they should be kept under observation and the blood examined at intervals of at least every 3 months to detect the earliest reappearance of the anemia and avert further progress

Treatment of Iron Deficiency Anemia

Iron

The treatment of these anemias is a relatively simple matter, if two guiding principles are kept constantly in mind namely, (1) iron is effective only when there is a deficiency of the metal in the body, (2) satisfactory results will be attained only provided an adequate dose of iron is prescribed In the past the dosage often has been too small

The causes of an iron deficiency have been discussed already and need not be repeated here Before giving iron one should ask the question, 'Is there an iron deficiency present, and what is the cause of it'? It is usually unnecessary to give iron to a person for example, who previously has been in good health and then suffers the loss of a moderate amount of blood from acute hemorrhage The body ordinarily has sufficient iron reserves to permit the regeneration of approximately 800 c c of blood Hence if the loss does not exceed this quantity then nothing will be accomplished in the way of causing the blood to return to normal more rapidly by the administration of iron If the amount of blood lost is greater than 800 c c however then iron therapy probably will be of value In case of doubt following acute hemorrhage it is wiser to administer iron for it may be helpful and it cannot possibly do harm In other instances of acute bleeding as, for example, in a person with a peptic ulcer who suffers an extensive hemorrhage it is advisable to give iron for two reasons (1) the amount of blood lost may have exceeded 800 c c, and (2) there may have been chronic hemorrhage over a long interval with occult blood in the stools and hence the iron reserves may have been depleted prior to the occurrence of the acute hemorrhage

If it is considered advisable to give iron then the preparation dosage and mode of administration must be determined In the first place let me say unequivocally and emphatically that the only method of administering iron to be recommended is the oral route This is because satisfactory results in my experience always have been attained by this method, and furthermore, if iron is

therapy alone where an operation can be performed safely On very rare occasions it may be proper to administer one or two blood transfusions in order to shorten the period of hospitalization and expedite the patient s recovery

Prognosis of Iron Deficiency Anemias

This varies with the type of iron deficiency anemia which is present In the nutritional anemia of children in chlorosis and idiopathic hypochromic anemia of women the effect of iron is prompt and all that is to be desired It should always be remembered however that these conditions are characterized by an ever present tendency to recur although in the case of female adults this frequently disappears after the menopause Iron medication should be continued for long periods of time and the patients observed in the case of women and children until there are no longer excessive demands for iron such as those associated with growth menstruation pregnancy and lactation

In the variety of anemia due to chronic hemorrhage the outlook is of course dependent on the underlying cause of the bleeding The anemia always is amenable to iron therapy provided the loss of blood can be controlled Even in cases of blood loss due to malignancy as in carcinoma of the stomach for example the anemia often can be corrected almost completely for considerable periods of time by iron medication and the patient thereby benefited at least temporarily

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This dosage provides 0 3 grams (gr 5) daily, which is suitable for infants and children up to 2 years of age Twenty c c of this mixture may be given daily to children from 2 to 6 years of age and in those over 6 years of age the dose should be 24 c c daily All iron preparations are given preferably after meals in order to lessen the gastrointestinal irritation Some prefer to take it in milk

Other preparations of iron which I have used successfully are a 50 per cent solution of ferric and ammonium citrate one teaspoonful 3 times daily which gives a total daily dose of 6 0 grams (gr 90), and ferrum reductum in doses of 0 5 grams (gr 7½) 3 times daily, which gives a total dose of 1 5 grams (gr 22 5) daily

If the results from iron therapy are not apparent and satisfactory within 10 days or 2 weeks one should reinvestigate the patient s condition and be reassured that an iron deficiency is actually present, and that the medication is being administered in the proper amounts If the condition is not benefited by 0 6 gram of ferrous sulphate 3 times daily, it is unlikely that larger quantities will be helpful Other possible explanations of the failure which should be investigated are a continuation of excessive bleeding which may result in more blood being lost than is being regenerated the presence of hypothyroidism a diet inadequate in vitamins proteins and mineral salts the presence of an infection or nitrogen retention, which may be observed in disturbances of the urinary tract

Hydrochloric Acid

Even in patients with an achlorhydria it is ordinarily not necessary to administer hydrochloric acid This is because with iron medication and the regeneration of hemoglobin to a normal level the digestive symptoms disappear without other medication If the gastrointestinal complaints continue then a careful investigation should be made to eliminate cholecystitis cholelithiasis or some other type of abdominal disturbance which might be responsible for the condition If nothing can be discovered there is no harm in giving 4 c c of dilute hydrochloric acid U S P in a full glass of water with meals 3 times daily

Blood Transfusions

Rarely are blood transfusions indicated in patients with iron deficiency anemias because the results from iron therapy alone are so prompt and satisfactory They should be given however if the hemoglobin level is so low as to endanger life which it rarely is or if the clinical picture is complicated by the presence of a severe infection such as lobar pneumonia Also in some instances such as an emergency operation, transfusions are justifiable when this procedure cannot be delayed a sufficient period of time for the blood to be brought to the level with iron

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28 HEATH C W and PATEK A J, JR Anemia of iron deficiency Medicine 1937 XVI 267
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fessor Anton Biermer of Zurich which followed Addison's second report by 17 years comes nearer the mark in giving an accurate description of the disease than any other which had appeared previously His report in the Correspondenzblatt fur Schweizerische Aertze Jahrgang 11 1872[4] is the most complete one but an earlier description had been given in the autumn of 1868 before the Dresdener Naturforscherversammlung The contributions of Biermer may be summarized as follows (1) he gave the disease its name progressive pernicious anemia (2) his efforts directed the attention of the medical profession throughout Europe and indirectly in the United States to the malady and hence it was the beginning of a more widespread interest in the condition (3) he gave an adequate description of the symptoms of the anemia and deserves special credit for pointing out initially the highly important fact that the patients frequently had a *yellowish white color without icterus* and that often purpura and retinal hemorrhages were present (4) he also noted that although emaciation might be present it was not unusual to have the subcutaneous fat retained and (5) that almost always hemic murmurs usually systolic in time might develop during the course of the disease

Other historic dates relating to the disease are as follows Samuel Fenwick in 1877[5] first observed that the mucous membrane of the stomach showed pronounced atrophy Although the earliest descriptions of the recurrent glossitis were by Barclay in 1851[6] and by Laache in 1883[7] its clinical significance was not recognized until William Hunter commented on it in 1889[8] According to Castle[9] Grawitz and others first recognized the importance of the achlorhydria It is known that Martius in 1897[10] also discussed this finding Its diagnostic value was emphasized in more recent years by Faber and Bloch[11] and by Levine and Ladd[12] Among those who first recognized that the achlorhydria persisted despite the hematological remissions was Hurst in 1923[13]

Probably Laache[7] in 1883 was the first to describe accurately the blood changes in terms of modern hematological technic It was he who recognized the importance of the large deeply colored macrocytes in the circulating blood and considered them to be the main distinctive hematological feature in this type of anemia Microcytes were first noted by Eichhorst[14] in 1887 and poikilocytosis by Quincke[15] in 1876 It was Paul Ehrlich in 1880 who first placed the hematology of pernicious anemia on a firm basis

Additional observations which are important from a historical standpoint are Klein[16] in 1891 recognized the importance of heredity when he reported the disease as occurring in four members of one family a sister and three brothers The literature in regard to this phase of the disease is reviewed by Stamos[17] The relationship between the disease and *dibothriocephalus latus* was first described by Reyher in 1884 and Runeberg in 1888 The earliest study of the bone marrow was made by William Pepper[18] in 1875 and a monograph dealing with this

PERNICIOUS ANEMIA

Synonyms — Addisonian anemia, Biermer's anemia Primary anemia

Definition — A macrocytic anemia, usually occurring in adults, considered to be due to a failure of the glands of the fundus of the stomach to secrete a sufficient quantity of a thermobile, enzyme like substance, which is thought to be essential to the normal maturation of the red blood cells The condition is characterized clinically by the symptoms and signs of anemia, a frequently associated paresthesia of the hands and feet recurrent glossitis, degenerative changes in the peripheral nerves and posterior and lateral columns of the spinal cord and a constantly occurring achlorhydria It always progresses to a fatal termination usually with remissions, unless specific therapy is employed

History

The earliest description of pernicious anemia is generally credited to Thomas Addison by the English speaking people of the world, and reference is made to his remarks dealing with the disease which appeared in the introduction to his well known monograph On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules published in 1855 It was while he was attempting to throw some light on the nature of true Addison's disease or adrenal cortical insufficiency that he described briefly a completely different syndrome namely pernicious anemia as we know it today This was not Addison's initial reference to the disease because 6 years before in 1849 in a paper read before the South London Medical Society on "Anemia Disease of the Supra renal Capsules', which was published in the London Medical Gazette for March 1849[1], he first mentions the malady but does not differentiate clearly between it and adrenal insufficiency According to Stephen MacKenzie[2] reference to idiopathic anemia had been made by Addison in his clinics several years before the appearance of this initial publication in 1849

While undoubtedly Addison deserves credit for depicting the syndrome it is known that similar cases had been recognized previously Credit for the earliest descriptions of the disease is difficult to assign because it is not possible in many instances to decide definitely if the author was actually describing the disease as we know it Although in England priority is given to the description of Combe (1823) and Addison (1849) as Coupland says[3] some consideration must be accorded the reports by Andral in 1823 Marshall Hall in 1837 Piorry in 1841 and Pearce in 1845

It is obvious to any present day hematologist that the description of Pro-

The momentous investigations of William B. Castle and his collaborators which began in 1929[3] and have continued to the present time, have led to an appreciation of the role of the stomach in the etiology of the disease. These experiments, brilliantly planned and executed, for the first time threw light on the cause of pernicious anemia by demonstrating the importance between the deficiency of some unidentified substance in the gastric secretions and the anemia in this disease. Furthermore they have also directed attention to the relationship between the diet, the gastric secretions, the liver and normal hematopoiesis. The results of Castle's experiments are epoch making and will continue for all time to be counted among the greatest advances in the study of disease processes. The information thus made available served in part to direct the attention of Sturgis and Isaacs[4] to the normal stomach as a possible source of antipernicious anemia medication. This led to the introduction of ventriculin in 1929[4] which has proved to be an effective form of medication in the management of the disorder.

Etiology

Frequency

Pernicious anemia is a disease of relatively common occurrence in North America, for in every general hospital there are usually 3 or 4 patients with the condition out of every 1 000 admitted. At the Henry Ford Hospital in Detroit this proportion was 2.2 per 1 000,[5] whereas at the Peter Bent Brigham Hospital in Boston between the years 1913 and 1932 the figure was 6 per 1 000. The incidence in the population at large is given as 6.9 per 100 000 in the United States, 9.0 in Canada and 9.18 in Sweden by Askanazy.[6]

There are two obvious explanations for the apparent increase in incidence in recent years as follows: (1) accurate diagnostic methods are employed more widely, and (2) as a result of increased longevity a greater number of persons now survive to the age when pernicious anemia is prevalent.

Age

The largest number of cases are observed in persons between the ages of 45 and 60 years. It should be emphasized, however, that the condition is actually a disease of old age. This can be demonstrated if the ages of patients with pernicious anemia are plotted against the number of persons living in each decade. Such a curve indicates that the percentage of cases increases with each decade. The actual number of cases, however, naturally decreases as the number of persons living in each decade is much less in the older age groups.

aspect of the disorder was published in 1876 by Julius Cohnheim The original observations on arsenic as a therapeutic agent were made by Byron Bramwell in 1877[19] Pye Smith in 1882 suggested that gray hair was observed very commonly in patients with this disease[20] Apparently the initial observations on the changes which may occur in the nervous system in this disorder, were made by O Leichtenstern in 1884[1]

Origin of the Liver Treatment

The introduction of liver therapy in the effective treatment of pernicious anemia constitutes a major therapeutic contribution in the history of medicine All credit must be accorded George R Minot, George H Whipple and William P Murphy for the introduction of this remarkable form of treatment into clinical medicine

The initial public utterance concerning liver therapy in this disorder was a brief reference to the topic made by Minot at a meeting of the Suffolk District Medical Society in Boston Massachusetts, on the evening of April 28, 1926 The first actual formal presentation dealing with the effect of liver in patients with pernicious anemia was by Minot before the Association of American Physicians at Atlantic City on May 4, 1926 This was not distributed in the printed form as part of the Transactions of the Association for that year until after an article by Minot and Murphy entitled "Treatment of Pernicious Anemia with a Special Diet" had appeared in the Journal of the American Medical Association for August 14 1926 Another similar article by the same authors was printed in the Boston Medical and Surgical Journal for August 26 1926

There can be no question but that the use of liver in the treatment was brought to the attention of clinicians in 1920 by the convincing experimental work of George H Whipple, then Professor of Research Medicine and Director of the Hooper Foundation for Medical Research, Medical School of the University of California and since 1921 Dean and Professor of Pathology at the University of Rochester Rochester, New York In the paper published in collaboration with F S Robscheit and C W Hooper dealing with the effect of various dietary substances on the regeneration of blood in dogs who had been made anemic by repeated experimentally produced hemorrhages the following statement was made, "cooked liver is able to induce blood regeneration even under the most unfavorable conditions" It was concluded from this work that cooked liver was as effective as meat in this respect and that "it may be even more efficient in promoting complete regeneration subsequent to a standard anemia"

Of greatest practical importance in the treatment of patients with pernicious anemia was the introduction of a refined and highly potent liver extract by Edwin J Cohn and his associates[22] in 1928 This is now the most satisfactory form of therapy, when given intramuscularly which is available at the present time

The momentous investigations of William B Castle and his collaborators which began in 1929[3] and have continued to the present time have led to an appreciation of the rôle of the stomach in the etiology of the disease These experiments brilliantly planned and executed for the first time threw light on the cause of pernicious anemia by demonstrating the importance between the deficiency of some unidentified substance in the gastric secretions and the anemia in this disease Furthermore they have also directed attention to the relationship between the diet the gastric secretions the liver and normal hematopoiesis The results of Castle s experiments are epoch making and will continue for all time to be counted among the greatest advances in the study of disease processes The information thus made available served in part to direct the attention of Sturgis and Isaacs[4] to the normal stomach as a possible source of antipernicious anemia medication This led to the introduction of ventriculin in 1929[4] which has proved to be an effective form of medication in the management of the disorder

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Age

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It is unlikely that true pernicious anemia occurs in infancy or childhood although cases have been reported in the first 10 years of life It is my opinion however, that such patients are suffering more likely from some other form of macrocytic anemia such as that due to diminished intake of the extrinsic factor to liver disease, to subleukemic leukemia to hemolytic anemia or to aplastic anemia The youngest bona fide case I have observed was in a girl of 19 years who had experienced her earliest symptoms 3 years previously

Geographical and Racial Distribution

It has been established clearly that this disease has a racial and therefore a geographical distribution It is distinctly a malady which has a predominance in the white race of the temperate zone Hence it is more prevalent in England Wales Scotland Ireland Germany, France, the Scandinavian countries Canada and the northern part of the United States Less commonly is it een in the countries of southern Europe and South America It is unknown in the natives of the tropics and is observed rarely in Asiatics Egyptians and Chinese

The general opinion is that the condition never occurs in full blooded negroes although it is known to occur in mulattoes It was observed in 9 negroes in a large group of patients studied at the Johns Hopkins Hospital by Evans but all of his cases were mulattoes The opinion is held by Granady [8], however that the condition is not as uncommon in this race as has been supposed previously

Of interest from the standpoint of racial and geographical distribution are the observations by Smith [9] and Apperly[30] that pernicious anemia is more likely to occur in areas where the solar radiation is less than in regions where it is normal or excessive These observations, however, have not been confirmed by Th ersch[31] by his studies in South Australia

Heredity

In more recent years it has been established that the disease has a definite familial incidence, and it is accepted that heredity plays a rôle in the etiology of the condition It has been estimated by Davidson and Gulland[32] that the possibility of any one individual acquiring pernicious anemia by chance alone is 1 in 20,000 Examples of the condition occurring in a number of blood relatives therefore, are overwhelmingly' in favor of a familial incidence as opposed to chance It is generally stated that in 10 to 20 per cent of the cases another instance of the malady is present among the blood relatives In reviewing our 645 cases at the Simpson Memorial Institute some years ago however Stamos[33] found a familial incidence of only 7 9 per cent This was thought to be an under

estimate as it is not always possible to obtain definite information in regard to the cause of death or disability in other members of the family In this group there were 3 families in which 3 of the children had the disease and in 5 additional families there were cases in 3 or more persons in successive generations among the lineal or collateral descendants In one family there were identical twin sisters the only siblings age 35 years who had the disease In our group of patients it was determined that 27 3 per cent replied in the affirmative that there was another case in the family when asked if anemia was present in any of their blood relatives

Previous studies on the incidence of achlorhydria in relatives have been summarized by Askey[34] and he confirms the conclusion that anacidity is more common among the relatives of patients with this disease than in the population at large He found for instance that there was an increased incidence of anacidity particularly among the blood relatives in the 2 decades prior to the age of 40 years and about a double percentage of it among the near relatives as opposed to distant relatives

More information is necessary before definitive conclusions can be drawn regarding the precise nature of the hereditary trait which is transmitted The view has been submitted but it is unproven that the malady is transmitted as a dominant characteristic dependent on a single gene and that there are members of families who do not have the active manifestations of pernicious anemia but act as carriers It is believed by some that there is a hereditary defect in the stomach which is transmitted from one generation to another The occurrence of cases of pernicious anemia and idiopathic hypochromic anemia in the same family in a greater incidence than can be accounted for on a fortuitous basis suggested that they may have a common inherited cause The literature in regard to this association is summarized by Heath[35]

Physical Factors

It has long been established that persons with light hair a fair complexion and the eyes of the lighter colors are more prone to have the condition than those who are dark complexioned Gray hair is known to occur more frequently in patients with the disease than in persons of equal age and there is often a familial incidence of prematurely graying of the hair It has been reported by Hardgrove and his associates[36] that 14 per cent of their group of patients had gray hair before the age of 30 years Draper[37] contends that patients with pernicious anemia have a tendency toward acromegalic facies but this has been questioned by Bauer[38]

While it must be admitted that persons with certain physical features are more likely to have the disorder it should be emphasized that the disease is not limited by any means to such persons

Present Day Theories Relating to the Etiology of Pernicious Anemia

For many years there have been two main views concerning the mechanism of the production of the anemia of pernicious anemia. The one championed by Cohnheim and by Ehrlich regarded the changes in the bone marrow as the primary cause of the anemia, the other supported especially by William Hunter in England held that the anemia was due primarily to an increased destruction of blood. With the modern development of our knowledge in respect to the etiology of the disease it is now accepted generally that the anemia of the disorder is primarily due to a maturation defect in the bone marrow. Increased destruction of red blood cells, if it occurs at all, is a mechanism clearly of secondary importance. The views regarding the possible importance of the hemolytic factor are summarized by Dock[39] and Bloomfield[40].

The etiology of pernicious anemia now seems to be solved, in part at least, by the remarkable and illuminating investigations of William B. Castle and his associates[41, 42]. It has been demonstrated by these investigators that the normal fasting gastric contents contain a principle, the intrinsic factor, which, when administered with beef muscle, the extrinsic factor, to patients with pernicious anemia, causes an increase in blood production and clinical improvement in the patient. As a result of this reaction in the stomach it is assumed that the anti-pernicious anemia or erythrocyte maturing factor (E.M.F.) is formed. This is absorbed apparently in the upper gastrointestinal tract and stored in the liver and possibly elsewhere. It is thought that the chief function of the E.M.F. is to control the rate of maturation of the red blood cells in the bone marrow.

In pernicious anemia it has been shown that there is atrophy of the glands of the fundus of the stomach[43, 44, 45] with a resultant deficiency of secretion of the intrinsic factor. This has the effect of reducing the amount of E.M.F. which is produced and consequently the rate of maturation or production of the erythrocytes in the bone marrow is diminished. As blood destruction proceeds at a normal or perhaps an accelerated rate, the number of red blood cells in the circulating blood must eventually diminish below the normal level and hence an anemia develops.

It is obvious that if a deficiency of the extrinsic factor occurs as a result of some dietary deficiency, then also a macrocytic anemia would develop. This possibly happens in sprue and in pellegra or in persons who are on an inadequate diet, especially with respect to protein. Furthermore, even if the extrinsic and intrinsic factors were present in normal amounts, there might be a deficiency of E.M.F., if there were some disorder of the intestine as stenosis or abnormal anastomoses which interfered with the normal absorption of the intestinal contents, and if there were widespread liver damage which prevented the normal storage of the E.M.F. The latter condition probably explains the macrocytic

anemia which sometimes is observed in cirrhosis of the liver It is generally conceded that in pernicious anemia the primary cause of the anemia is a decrease in the amount of intrinsic factor but in addition it is probably true that the diminution in the extrinsic factor in the diet may also play a role in some patients but one of secondary importance

It has been reported by Spies and his associates[46] that when synthetic folic acid (*L Casei* factor) is given parenterally or orally to patients with a macrocytic anemia there is a significant hemopoietic response This is evidenced by an increase in the number of reticulocytes and in the hemoglobin and red blood cells which are comparable to the increases observed following the injection of potent liver extract *intramuscularly in patients with pernicious anemia* In a second paper by Vilter and his associates[47] it is reported that synthetic folic acid is effective in treating the macrocytic anemia of pernicious anemia pellagra sprue and pregnancy All of these anemias according to these authors responded to either the parenteral or oral administration of synthetic folic acid Synthetic folic acid (*L Casei* factor) was administered to 14 patients with macrocytic anemia *in relapse The group included both Addisonian pernicious* anemia and nutritional macrocytic anemia The material was given intravenously intramuscularly and orally Erythrogenesis occurred regardless of the route of administration of folic acid and regardless of the clinical classification as to pernicious anemia macrocytic or nutritional anemia

In the opinion of these authors the responses to treatment paralleled those produced by potent liver extract In 13 of the 14 patients treated there was a positive hematological response consisting of a reticulocytosis and subsequent rise in hemoglobin and erythrocytes

The authors conclude that at present it appears that synthetic folic acid is *effective as a hemopoietic agent of itself but studies have not progressed to the* point that would warrant a statement concerning the relation of folic acid to the intrinsic or extrinsic factors They do not anticipate that synthetic folic acid will have a curative effect above and beyond that afforded by potent liver extract since the original compound was isolated from liver The possibility exists however *as suggested by Spies*[47, 1] that folic acid occurs in many foods as a conjugate and that in patients with pernicious anemia there may be a deficiency of the enzyme perhaps the intrinsic factor of Castle which liberates it Carrying this hypothesis further it is possible to assume that the material thus liberated is not the erythrocyte maturing factor (E M F) but by the action of the intrinsic factor it is transformed to such a state that it can be absorbed from the gastrointestinal tract It may then be converted in the liver to the E M F and in this form control the rate of maturation of the red blood cells in the bone marrow The discovery that folic acid is effective in the control of the anemia of pernicious anemia and allied conditions constitutes one of the greatest recent contributions

to our knowledge of the nature of the macrocytic anemias At present all of the facts regarding the action of this remarkable substance are not known, but it is reasonable to predict that in the next few years important information which has a bearing on the etiology and treatment of this type of anemia will be forthcoming

Recently Bethell and his associates [47(b), 47( )] have made significant observations on the behavior of folic acid in the body, which has an important bearing on the relation of this substance to the etiology of pernicious anemia Their experiments show that a normal person can convert vitamin B conjugate to the free form whereas a patient with pernicious anemia in relapse is unable partially or totally, to liberate the free vitamin from its conjugated state Furthermore these studies have shown that during remission induced by liver extract, patients with pernicious anemia acquire the ability to convert the conjugated vitamin B to the free form These observations suggest that the defect in a patient with pernicious anemia is one concerned with the inability to process, convert store or make available the free form from the conjugated variety

Further studies by these investigators indicate that patients who have had a total gastrectomy with a resultant macrocytic anemia are unable to convert the conjugated folic acid to the free form Furthermore it has been shown that the normal human gastric juice does not contain a conjugase and hence is incapable of converting conjugated folic acid to its free state

With these facts in mind Bethell and his associates have suggested the following tentative hypothesis relating to the etiology of pernicious anemia In a normal person the extrinsic factor of the diet reacts with the intrinsic factor in the gastric juice to form the erythrocyte maturing factor The latter (E M F) functions as a conjugase and hence is capable of releasing the free form of folic acid from the conjugated variety in the food Folic acid thus liberated, acts to control the maturation of the red blood cells in the bone marrow

When the cells develop at a normal rate they are set free into the circulating blood in such numbers as to compensate for those which are destroyed normally and the red blood cell count remains at a normal level In a patient with pernicious anemia, on the other hand, there is a diminution in the amount of the intrinsic factor, and consequently the erythrocyte maturing factor is not produced in these patients in a normal quantity As a result the conjugate form of folic acid in the food cannot be split as it is in the normal person, and the required amount of free folic acid is not liberated Thus free folic acid the factor which controls the normal rate of development or maturation of the red blood cells in the bone marrow, is deficient in amount, and the maturation process becomes arrested at least in part When this occurs the number of erythrocytes, which are released to the circulating blood is diminished and consequently an anemia develops This theory is formulated from new and reliable information, upon

which a plausible hypothesis has been based Further studies however may cause a revision of the view presented hence it should be considered as a purely tentative hypothesis which can be altered as new information becomes available

The chemical composition of the extrinsic or intrinsic factors is unknown at present It is recognized that the intrinsic factor is not any of the known ferments and that it is probably an enzyme which functions best at a pH of 7.4 or 7 7 It is known to be heat labile being destroyed when exposed to a temperature of 70° to 80 C for one half hour

The nature of the extrinsic factor is unknown despite the careful studies of Castle and his associates[48] These investigators conclude that it is reasonable to continue to regard the extrinsic factor as being a thermostable component of the vitamin B complex which as yet has remained unidentified In my own opinion it seems to be some substance which is loosely identified with the protein intake of the diet

It is not possible at this time to make a positive statement concerning the exact chemical nature of the active principle in liver (E M F) despite the large amount of careful work which has been done It is regarded as a peptid by Dakin Ungley and West[49 50] and others[51] Karrer[41] found it to contain carbon 45 6 per cent hydrogen 6 7 per cent and nitrogen 14 6 per cent This observer noted first that the ninhydrin reaction was strongly positive the biuret test weakly positive and the amino acid nitrogen content was 0 75 to 0 9 per cent

It has been concluded by Erdos[5] that the active principle liver is an amino acid complex containing three COOH groups it contains sulfur and phosphorus it is soluble in water acids and bases it precipitates with alcohol concentrations greater than 87 per cent and it has a molecular weight of 6 000

The most comprehensive summary of the literature bearing on the composition of the active principle in liver is given by Subbarow Hastings and Elkin in an article with a bibliography of 129 articles dealing with the subject[52] They tabulate the chemical properties of the various liver preparations to which activity has been attributed and comment on their great variation The latter they explain by stating that the materials which have been studied are not pure preparations but are more or less contaminated They conclude with the following statement Although it is not yet possible to present the chemical properties of the antipernicious anemia material from liver with chemical exactness it is nevertheless proper to note that during the seventeen years since whole liver therapy has been introduced the amount of material needed by the patient per day has decreased from 400 grams to less than 1 milligram Such progress makes it reasonable to expect the isolation and identification of the active material to be an attainable objective

Attempts to Produce Pernicious Anemia Experimentally

If Castle's theory is correct, it would appear logical to attempt to reproduce the disease in animals by total gastrectomy This however, has never been accomplished In an extensive review by Ivy[54], written in 1940, it is stated that all attempts to reproduce the blood and bone marrow changes of pernicious anemia in animals by gastrectomy and dietary modifications have failed Furthermore, he has no faith in the few reports to the contrary which appear in the literature This view is supported by a comprehensive survey of the literature by Petri and Jensenius[55] It is the opinion of these latter authors that the failure to produce pernicious anemia experimentally in animals may be due to (1) the nonexistence of this type of anemia in animals, (2) the production of the intrinsic factor in the duodenum and perhaps other parts of the gastrointestinal tract or (3) the possibility that a disturbance of some unknown factor or factors is required in addition to gastrectomy and duodenal resection

On the other hand it is known that total gastrectomy in humans sometimes is followed by a macrocytic anemia which is identical in all respects with the true pernicious anemia type The literature dealing with this topic is summarized by Meyer Schwartz and Weissman[56] They conclude that (1) the symptoms and typical hematological picture develop within 2 to 15 years after the operation (2) evidences of subacute combined degeneration of the spinal cord often accompany the anemia (3) gastrointestinal symptoms are observed almost always, (4) the response to antipernicious anemia therapy is specific and dramatic

Etiology of the Manifestations Other Than the Anemia

The cause of the neurological changes in patients with pernicious anemia is unknown The most acceptable theory concerning this at present is to regard the degenerative changes in the nervous system as due to some deficiency of diet or the failure to absorb some essential article of diet as a result of the constantly present achlorhydria There is no conclusive evidence as to just what this hypothetical constituent of the diet may be, but it is logical to consider it as some unidentified member of the B complex

The cause of the recurrent attacks of glossitis likewise is unknown but here also it is a plausible assumption to consider that it results from some deficiency of a member of the B complex as Middleton[57] has emphasized

The cause of the premature gray hair of patients with pernicious anemia has never had a satisfactory explanation but it is very tempting to speculate over the possibility that perhaps some substance such as para amino benzoic acid or pantothenic acid claimed by some to be related by a deficiency to gray hair might play a role in the production of this change in patients with pernicious

anemia Here again these substances might not be lacking in the dietary intake but fail to be absorbed in normal amounts on account of the achlorhydria

Summary of Modern View of Etiology of Pernicious Anemia

In summary the following statements may be made in regard to the etiology of pernicious anemia On the basis of definite proven experimental observations and anatomical findings it seems clear that the anemia of pernicious anemia is the result chiefly of the inability of the glands of the fundus of the stomach to secrete an adequate amount of the intrinsic factor and possibly to a minor extent to a decreased dietary intake of the extrinsic factor in some cases An increased rate of red blood cell destruction possibly plays a role of secondary importance in the production of the anemia Largely on a speculative basis it is tentatively suggested that the spinal cord changes the recurrent glossitis and possibly the premature graying of the hair may be attributable to a dietary deficiency or a malabsorption of some article of diet possibly some components of the vitamin B complex The exact role of folic acid in the etiology of the disease has not been determined as yet

PATHOLOGY

Before the modern treatment of pernicious anemia was introduced in 19 6 when patients with this disease usually succumbed at a time when the anemia was severe the commonly observed findings at necropsy were as follows Evidences of the anemia widespread fatty degeneration of many parenchymatous viscera and muscles a predominance of megaloblasts in the bone marrow interpreted by a majority of the present day pathologists as a maturation arrest of the red blood cell series at the megaloblast stage deposits of hemosiderin an iron containing pigment derived from hemoglobin in the liver spleen and kidneys degenerative changes in the peripheral nerves and in the posterior and lateral columns of the spinal cord The changes in the stomach consisting largely of atrophy of the mucosa in the fundic zone are now thought to be constantly present and it is indeed perhaps the sole absolutely typical finding in the disease from the standpoint of the pathologist it is discussed in detail on a later page Hence until the changes in the stomach were established as a specific lesion there was no single pathological alteration which could be recognized as distinctive of pernicious anemia Pathologists in the past have arrived at the anatomical diagnosis by excluding other various recognized causes of anemia and by noting a combination of the findings enumerated above

Due to the effectiveness of antipernicious medication patients now rarely die at a time when the anemia is advanced Hence the anatomical findings at present are not often those of a severe anemia but more frequently those of some

coincidentally associated disease such as cancer of the stomach, hypertension or some other lethal condition unrelated to pernicious anemia or evidences of an advanced degenerative lesion in the nervous system with a complicating severe infection of the urinary tract, the characteristic atrophy of the mucosa of the fundus of the stomach and variable changes in the bone marrow depending on the severity of the anemia at the time of death

Of special interest are the findings in the stomach, bone marrow and nervous system The characteristic gastric alterations are summarized by Cox[58], who states that there is thinning in the region of the fundus due to an abnormal type of mucosa in which the parietal and chief cells the normal cell types, are absent According to this investigator the mucosal glands are shorter, less numerous and more tortuous than those normally present in the fundic region

When the bone marrow of patients with pernicious anemia in relapse is studied the most constant change observed is the increase in the number of nucleated red blood cells from the average of about 20 per cent to 35 or 50 per cent The most characteristic finding is the presence of megaloblasts which may make up from 20 to 30 per cent of all the marrow cells Such a megaloblastic marrow is observed in pernicious anemia, achrestic anemia and certain nutritional anemias such as sprue In almost all other types of anemia the predominating type of cell is the normoblast

The initial lesion in the nervous system is a swelling of the myelin sheaths localized to a small area of white matter, which progresses to an outspoken fatty degeneration, and finally destruction of the axis cylinders The degenerative change usually begins in the posterior columns of the lumbar portion of the spinal cord as scattered foci and gradually spreads upward and downward The involvement is not systemic in nature as it does not affect the long fiber tracts in the posterior and lateral columns uniformly throughout their length Furthermore it should be emphasized that the characteristic change is not limited to the posterior and lateral tracts of the cord, but the peripheral nerves[59 60 61] and the white matter of the brain likewise may be involved[59]

It should be recognized that the degenerative changes in the nervous system are in no sense an inflammatory reaction, and furthermore there is no spontaneous attempt to repair the lesion by the organizing function of the glial tissue No dense glial scar formation is observed and hence the term "combined sclerosis is a misnomer and should be abandoned It is claimed however, by Davison[62] that with liver therapy there is glial proliferation which replaces the destroyed tissue

Symptoms

The complaints of patients with pernicious anemia may be divided conveniently into four main groups those referable to (1) the anemia (2) the gastro-

intestinal tract (3) the nervous system and (4) the cardiovascular system In almost all patients there are usually complaints of varying degree representing each group

The onset of the disease usually is insidious and hence it is often impossible for the patient to state accurately the exact time when the first evidences of the malady appeared In about one third of the cases the earliest symptoms are referable to the anemia These consist of ease of fatigue weakness pallor and dizziness Cardiovascular manifestations which are also due mainly to the anemia are the first indication of the disease in about 10 per cent of the patients These are palpitation and dyspnea on exertion and occasionally cardiac pain which may be suggestive of angina pectoris In about one third of the patients the onset is characterized by gastrointestinal complaints such as anorexia nausea vomiting mild epigastric discomfort and either constipation diarrhea or an alternation of the two It should be kept in mind that gallbladder disease is not uncommon in patients with pernicious anemia and hence this may be the basis for certain of the gastrointestinal symptoms In about 25 per cent of the patients the onset is with neurological manifestations and of these the one which is most constantly encountered is persistent numbness and tingling of the hands and feet Others are weakness and spasticity of the muscles of the lower extremities due to involvement of the lateral columns of the spinal cord ataxia resulting from degenerative changes in the posterior column of the cord and loss of control of the sphincters of the urinary bladder and less frequently of the rectum Occasionally muscle tenderness is present possibly as a result of involvement of the peripheral nerves

The usual history is one of a very gradually developing weakness which becomes progressively worse until the patient is no longer able to continue working Commonly associated with this are gastrointestinal complaints most frequently anorexia which in many instances is extreme When the physician is first consulted the weakness usually has not reached the point which has made bed rest imperative and ineffectual efforts may still be made by the patient to carry on his normal daily activities In many instances it is amazing that patients with such severe degrees of anemia have sufficient strength to accomplish as much as they do Coincident with the appearance of weakness and fatigue there is a gradually developing pallor which often has a slight yellowish tint as the anemia becomes pronounced

Of unusual diagnostic significance is the history which is present in about two-thirds of the patients that they have recurring attacks of sore tongue which may be in some instances the sole initial complaint Although the statement that recurring glossitis is present should at once suggest the diagnosis of pernicious anemia the condition is not specific for this disorder It is known to occur also in idiopathic hypochromic anemia the anemia of pregnancy sprue pellagra the

Vinson Plummer syndrome, malnutrition associated with dysentery and anemia intestinal stricture, diphyllobothrium infestation and in patients with achlorhydria due to other conditions The term ' recurrent" is very aptly applied to the condition, because it characteristically appears for a period of several weeks and then, without apparent reason, disappears spontaneously, only to reappear again after a variable period of one to several weeks or longer During the exacerbations the tongue often is extremely painful and has a fiery red color In some instances the discomfort is so intense as to interfere with the ingestion of food

A symptom of high diagnostic value is the presence of numbness and tingling of the hands and feet It occurs in fully 90 per cent of all patients with the disease and if absent, one considers seriously that the patient may have some other form of anemia It should be emphasized that the condition persistently involves all four extremities It usually begins in the feet and extends to the hands shortly thereafter While the intensity of the condition may vary from day to day it does not completely disappear spontaneously If the patient hesitates in admitting that the hands and feet "go to sleep', it is usually an indication that the true parasthesia of pernicious anemia is not present, as in this condition there is ordinarily no question in the patient s mind that it is present

Other complaints referable to the nervous system are due to the involvement of the posterior and lateral columns of the spinal cord With changes in the former there is ataxia with difficulty in walking and in standing without swaying As the lateral columns become involved, the patient develops varying degrees of muscular weakness of the lower extremities until finally there may be evidence of advanced degrees of spastic paraplegia With more extensive changes the sphincters of the bladder and in some instances, the rectum become involved with a resultant incontinence of urine and feces A matter of great practical importance is the loss of control of the urinary bladder sphincters which results in an inability to void normally with the development of a residual urine Eventually a cystitis develops there is an ascending infection of the pelvis of the kidneys abscesses of the kidney are formed septicemia may develop and a fatal issue in some instances follows

It has been stated from the earliest description of the disease that patients with pernicious anemia are well nourished despite the pallor which they have This is true in some instances probably because the patient was somewhat over weight at the onset of the anemia but patients with the disease and different degrees of nutrition are encountered A review of the weight loss experienced by our patients indicates that usually there is a loss of from 20 to 25 pounds during the course of their illness It is to be expected that their body weight will diminish as anorexia is a common complaint and often there is a slight amount of fever present especially when the red blood cell count is low Certainly it can

be said that the disorder is not confined to the obese but it does appear less commonly in persons who are underweight

Physical Signs

General Description

The important findings which may be present on examination of a patient with pernicious anemia are the good or fair state of body nutrition despite a yellowish pallor the smooth aspect of the dorsum of the tongue the gray hair a systolic hemic murmur the variable evidences of degenerative lesions in the nervous system from no alterations whatsoever to evidence of loss of vibratory sense or more extensive changes such as a spastic paraplegia and the absence or other clinical manifestations such as enlarged lymph nodes and splenomegaly

Patients with this condition usually appear well nourished although as previously stated there is often a history of a loss of 20 to 25 pounds during the course of the illness There are exceptions to this statement but emaciation is uncommon

The degree of pallor is directly related to the level of the hemoglobin of the circulating blood It varies from an intense degree characteristic of the pallor of death to that which approaches normal When the red blood cell count is below 2 5 million per cubic millimeter there is likely to be a delicate yellowish tint to the pallor which is related to an elevation of the blood bilirubin in the circulating blood It is possible that the yellowish tint of the pallor requires that the hyperbilirubinemia shall be of some duration because it is certainly not now seen with the same frequency as before the introduction of the liver treatment The color has been described as a lemon yellow tint or grapefruit color but it never assumes the deep yellow or orange hue of outspoken icterus When this does occur in a patient with pernicious anemia one should suspect biliary obstruction or that the patient has some variety of hemolytic anemia

The hair of the head of many patients with the malady is partially or completely gray and the original color most commonly has been light Likewise the eyes are frequently of the lighter shades of green gray or blue This is not always true however for typical examples of the disease may occur in persons with extremely dark complexions

The appearance of the tongue in about one half of the patients is highly suggestive of the disease Never in my experience have I seen a patient with proven pernicious anemia who had a heavily coated tongue This is even true when the patient may be critically ill with a pronounced anemia high fever and in a state when one would ordinarily expect a coated tongue to be present In some instances when complaints are referable to the tongue there may be a fiery red appearance to the tip or the entire organ may be involved In about one half

of the patients there is a smooth appearance over the dorsum of the tongue due to complete or partial atrophy of the papillae Usually it is diffuse in distribution but in some instances it may be localized The smooth appearance along the margins of the tongue should not be regarded as a significant change, as the papillae are usually absent in this area in normal persons

Heart and Lungs

Examinations of these organs usually disclose no abnormalities of importance In most instances the lungs are normal on examination In the terminal stages there are often rales present which are indicative of a pneumonic process It should be emphasized that tuberculosis is a rare complication of pernicious anemia

The heart usually is borderline in size, and when the red blood count is below 2 5 million per cubic millimeter, there is invariably a soft systolic, hemic murmur present Although diastolic hemic murmurs have been reported, they are so rare in my experience that they should be regarded as organic until otherwise proven

Abdominal Examination

The liver and spleen usually are not palpable although the older clinicians often reported that the spleen was enlarged in many patients with the disease In a review of our own cases however, Bigg[63] found that the spleen was palpable in only 3 of 200 patients In 18 of the patients in whom necropsies were performed the organ varied in weight from 95 to 640 grams with an average of 265 grams In 17 of the 18 patients it weighed more than the commonly accepted normal weight of 150 grams It may be said, therefore that moderate to slight splenic enlargement is present commonly at necropsy but rarely is the organ so enlarged that it can be palpated during life Hence the presence of a distinctly palpable spleen in a patient suspected of having pernicious anemia should arouse suspicion that some other condition such as leukemia cirrhosis of the liver or some variety of hemolytic anemia may be present

Abdominal examination in patients with pernicious anemia is important in order to exclude tumor masses which may be malignant in nature and thereby account for an anemia on another basis In some instances there may be striking abdominal distention in association with advanced changes in the spinal cord In other patients there may be tenderness in the right upper quadrant suggestive of gallbladder disease

Edema

This is not a common finding in patients with pernicious anemia, but slight pitting edema may be observed When present, it may be attributed to low

plasma proteins associated with a deficient protein intake to increased capillary permeability or to myocardial weakness

Fever and Secondary Thrombocytopenic Purpura

As the anemia becomes severe two signs may appear unless prompt therapeutic measures are instituted to avert them They are fever and thrombocytopenic purpura *When the red blood cell count falls to below 2 5 millions per cubic* millimeter and the hemoglobin level to the vicinity of 50 per cent fever due to the anemia itself is commonly present but it usually does not exceed 100° F orally when the red blood cell count falls below 1 million per cubic millimeter it may rise to 101 to 104° F at which time there is likely to be associated mental confusion or delirium Other causes of fever in patients with pernicious anemia should be kept in mind such as an infected urinary tract which is observed commonly in patients with advanced cord changes and urinary retention and a complicating cholecystitis

When the red blood cell count falls below 1 0 million per cubic millimeter there may be bleeding from the nose mouth and into the skin and retinae which occurs as the result of a thrombocytopenia As patients with this disease are not now permitted to have an anemia of such a low level persist for long interval due to the modern treatment such hemorrhagic tendency no longer is observed commonly

Neurological Manifestations

Evidences of involvement of the nervous system in patients with pernicious anemia may be classified conveniently into four main groups as follows (1) those with only parethesia of the hands and feet which is probably due to a peripheral neuritis (2) those with a parethesia and evidences of a lesion in the posterior *columns of the spinal cord (3) those with parethesia and symptoms and signs of* both posterior and lateral column involvement (4) those with the changes enumerated above plus loss of sphincter control In a majority of patients the order of progression of involvement is first the peripheral nerves then the posterior columns next the lateral columns and finally the loss of control of the sphincters

Evidence of involvement of the peripheral nerves is a persistent progressive symmetrical annoying but not painful numbness and tingling of the hands and feet *In some instances this may progress to the level of the midwaist* but usually it is confined to the arms and legs and does not extend above the elbows or knees Lesions of the posterior columns are indicated by loss of the sense of motion and position and impairment of the vibratory sense This almost invariably begins

in and usually is limited to the lower extremities, but in rare instances the arms may be involved also As a result of the loss of sense of motion and position ataxia is present, similar to that observed in a patient with tabes dorsalis, and difficulty is experienced in walking A valuable differential point from the latter condition is that in the subacute combined degeneration of the cord associated with pernicious anemia the deep pain sense is preserved, whereas it is almost always conspicuously absent in tabes

Lateral column lesions manifest themselves by varying degrees of weakness, spasticity exaggerated deep reflexes in the lower extremities a positive Babinski's sign and ankle clonus When the combined lesions are extensive that is, in the presence of definite involvement of both the lateral and posterior columns of the spinal cord then the patient has all of the evidences of a spastic ataxic paraplegia The degenerative changes in the spinal cord may progress to the degree that they produce the signs of a complete transverse myelitis Loss of control of the sphincters the urinary more often than the rectal, usually is accepted as evidence as a sign of extensive involvement of the posterior columns of the cord With progression of the neurological lesions and loss of control of the bladder sphincters a resultant stasis of urine in the bladder with eventual infection of the urinary tract and a cystitis are likely to occur If such a condition is not checked there may be an ascending infection of the ureters and kidney with a pyelitis, abscesses of the kidneys and in some instances, a terminal septicemia

In a study of a group of 408 of our patients with pernicious anemia[64] it was found that neurological manifestations were present in approximately 90 per cent Of these 45 per cent had the symptoms of nervous system involvement at the onset of the disease and in 46 per cent they developed during the course of the illness but before the patient came under our observation Evidence of combined degeneration was present in 40 7 per cent A tabulation of the neurological manifestations found in our group of patients is given in Table I

TABLE I

	Present Per Cent
A Posterior column manifestations	
Numbness and tingling	90
Ataxia in locomotion	74
Positive Romberg's sign	62
Decreased or lost vibratory sense	48
Bladder disturbance	46
Loss of position sense	42
Muscular atrophy	24
Ankle jerks decreased or absent	24
Knee jerks decreased or absent	18
Anaesthesia (to pain temperature or touch)	8
Cutaneous hyperesthesia	8
Sharp shooting pain	8

B Lateral column manifestations	
Positive Babinski reflex	56
Stiffness	42
Knee jerks increased	38
Ankle jerks increased	28
Biceps jerks increased	24
Triceps jerks increased	24
Spastic paralysis of legs	[illegible]
Ankle clonus	6
C Cerebral manifestations	
Irritability	64
Memory disturbances	60
Mild depression	58
Delusions	10
Coma	18
Hallucinations	[illegible]
Indifference of apathy	6
Violent maniacal outburst	

Table No I showing the incidence of neurological and cerebral manifestations in 50 cases of pernicious anemia in which special attention was directed toward the study of the neurological changes *It should be noted that one or more of the following abnormal findings were observed in over 50 per cent of the patients* numbness and tingling of the extremities 90 per cent ataxia 74 per cent positive Romberg's sign 62 per cent positive Babinski's sign 56 per cent irritability 64 per cent memory disturbance 60 per cent mental depression 58 per cent It should be taken into account however that these statistics are based mainly on a study of patients who were sent to the hospital because of failure to improve and hence it may be concluded that many were in the advanced stages of the disease The statistics also were collected some years ago before the extensive use of the more effective type of parenteral liver extract treatment was in wide spread use

The classification of the various manifestations into those attributed to changes in the posterior and lateral columns is an arbitrary one of convenience as it is appreciated that some of the clinical abnormalities may be due to changes in the peripheral nerves (Table modified from Goldhamer Bethell Isaacs and Sturgis Jour Am Med Assoc 1934 CIII 1663)

Laboratory Examinations

Changes in the Blood Cells

Red Blood Cell Count Hemoglobin Color Index — The red blood cell count varies from below 1 0 million per cubic millimeter to normal depending on the stage of the disease Symptoms arising from the anemia are slight when the red blood cell count is 3 5 millions per cubic millimeter or higher somewhat more pronounced when it is about 3 0 million and definitely incapacitating when it is 2 0 millions per cubic millimeter or less The lowest count I have observed in a patient was 480 000 per cubic millimeter which was subsequently restored to normal by liver therapy

The hemoglobin level is almost always relatively high and consequently the color index is 1 0 or more in patients with the uncomplicated disease who are un

treated Rarely is the color index low This may arise, if some complication is present such as chronic hemorrhage from one cause or another It is also below 1 0 in patients who are being treated with potent antipernicious anemia therapy during the first 3 to 6 weeks of the therapy This is because during this period the increase in the number of red blood cells is greater than the rise in the hemoglobin, hence the color index must fall In rare instances if there is an associated iron deficiency the color index will remain low, unless this form of therapy is administered but usually it returns to normal with antipernicious anemia medication alone

Changes in Size and Shape Macrocytosis Presence of Immature Erythrocytes — It is generally agreed that the most constant finding in the blood of patients with pernicious anemia is the presence of large oval erythrocytes which stain somewhat darker than the average red blood cell because they are thicker These cells are called macrocytes and they may make up from 20 to 30 per cent of all red blood cells in the circulating blood They vary from 8 5 to 15 microns in size, the latter being the average diameter of a mature neutrophil

A macrocytosis is recognized as the earliest change, which occurs in the blood as the anemia develops and it is the last to disappear, when the blood returns to normal To the trained hematologist the presence of macrocytes is the most constant sign in the peripheral blood of patients with the disorder and in the presence of an anemia the absence of such cells is considerable evidence against the diagnosis of true pernicious anemia

In addition to macrocytes the blood film of patients with this condition invariably shows microcytes, measuring from 3 to 5 microns, and bizarre shaped erythrocytes or poikilocytes Such changes are present always when the red blood cell count is below 3 5 millions and become progressively more conspicuous as the severity of the anemia increases

All forms of immature erythrocytes may appear in the blood of patients with pernicious anemia but they are never present unless the blood is in the regenerative phase Hence in the latter state one may observe normoblasts, more rarely megaloblasts an increased number of reticulocytes and cells showing punctate and diffuse basophilia As patients are less likely to consult a physician, when the blood is in the regenerative phase and hence the patient's condition is improving the immature cells are of little importance from the standpoint of diagnosis

Volume Measurement of Red Blood Cells and Their Hemoglobin Content — The average volume of the individual red blood cells in pernicious anemia during a relapse that is when an anemia is present, is always increased above normal This figure which is obtained by dividing the hematocrit reading by the number of red blood cells per cubic millimeter gives the mean corpuscular volume (M C V) which normally varies between 86 and 96 cubic microns In pernicious anemia it is increased and in general it may be said that the more

severe the anemia the greater the mean corpuscular volume Readings between 110 and 140 cubic microns are the rule There is one exception to this statement however and that is when the red blood cell count is below 1 0 per cubic millimeter At this level of the erythrocyte count there are often many microcytes and consequently the M C V may be lower than anticipated namely from 110 to 115 cubic microns

The relation of the hemoglobin content of the cells to their volume is best expressed by the mean corpuscular hemoglobin concentration (M C H C) which gives information similar to that derived from the color index The M C H C is calculated by dividing the hemoglobin in grams per 100 c c of blood multiplied by 100 by the volume of packed cells hematocrit reading in c c per 100 c c Normally this value is between 30 and 32 per cent in pernicious anemia it is between 30 and 35 per cent in hypochromic anemia it is below 30 and may be as low as 26 per cent

Price Jones Measurement — These measurements are made by determining the diameters of 200 red blood cells and charting them according to the percentage of cells with certain measurements This is an excellent procedure for indicating the presence of both microcytes and macrocytes and the size of the cell which predominates in numbers The blood of patients with pernicious anemia when the red blood cell count is below 2 5 million per cubic millimeter shows the following characteristic changes in the Price Jones curve (see Fig 1 in Vol II Chapt XV of Oxford Medicine) (1) microcytes measuring 3 to 4 microns in diameter and macrocytes having a diameter varying from 1 to 15 microns are present (2) the greatest number of cells are those having a diameter of 9 0 to 9 5 microns Determining the Price Jones measurements is however a more laborious procedure than determining the erythrocyte count and the volume determinations by means of the hematocrit and less accurate Consequently it is not employed routinely by most hematologists

LEUKOCYTES — An important and constant change in the blood of patients with pernicious anemia is a leukopenia due mainly to a diminution in the number of neutrophils One would hesitate to make the diagnosis of this disorder in the presence of a leukocytosis if a definite anemia is present and if antipernicious anemia medication has not been given Usually with a few days of treatment the white blood cell count increases to normal or slightly above and if an infection which ordinarily evokes a leukocytosis is present there may be a hyperleukocytosis in some instances reaching a total white blood cell count of 50 000 per cubic millimeter or more In patients in a state of relapse and without treatment the white blood cell count remains low despite the presence of an infection regardless of its severity

Another change of considerable importance from the standpoint of diagnosis is the constant presence of a predominating number of neutrophils with nuclei

having 4 to 6 lobes or more, indicating that they are older forms than are encountered ordinarily in the blood This has the effect of producing a "shift to the right" in the terms of the Arneth count

Blood Platelets — A decrease in the number of circulating blood platelets is observed constantly during relapse, and in general it may be said that the reduction is roughly proportional to the severity of the anemia In some instances in untreated patients the decrease is so pronounced that a secondary thrombocytopenic purpura develops After therapy the increase in the platelets parallels that of the erythrocytes The subject of the blood platelets in this disorder has been reviewed by Paddock and Smith[65] who conclude that thrombopenia although constantly present in pernicious anemia in relapse, is not a differentiating feature from other macrocytic anemias

Hyperbilirubinemia

It is generally recognized that when the anemia of pernicious anemia is present the blood bilirubin is increased above the normal level of 0 8 milligrams per 100 c c Furthermore it is known that the increase is roughly proportional inversely to the severity of the anemia It is the increased amount of this bile pigment in the circulating blood which imparts the lemon yellow tint to the skin and mucous membranes of patients with the disease In pernicious anemia the bilirubin may be increased during relapse to 1 0 to 3 0 milligrams per 100 c c of plasma, and the icterus index to 20 to 25 units depending on the level of the red blood cell count

In the past it has been held by some that the hyperbilirubinemia is an indication of increased blood destruction in this disease and so it might well be It is not necessarily so however for it may be due to some other cause perhaps the inability of the red blood cells to reutilize that amount of bilirubin released by normal blood destruction and hence it accumulates in the blood stream

Prothrombin Level of the Blood

The prothrombin level of the blood is somewhat below normal in this disorder according to the observations of Warner and Owen[66] These observers found when employing the two-stage method of Warner Brinkhaus and Smith that the level was between 40 and 65 per cent of normal in most patients The low level was not altered by the administration of vitamin K when given either orally or intravenously This leads them to suggest that the deficiency of prothrombin may be attributable to hepatic damage There was a tendency for the lowest prothrombin level to be associated with the most severe anemia The deficiency

of prothrombin may explain in some instances the tendency of patients to bleed abnormally although it is generally thought that this is due to a thrombopenia

Achlorhydria

An achlorhydria is the most constant finding in the disease and it is my opinion that the diagnosis of pernicious anemia should be eliminated if free hydrochloric acid can be detected in the gastric secretions Furthermore it is also true that there is an associated lack of pepsin in the gastric secretion in all cases Not only are these two statements true but it may be said that in addition in any patient with pernicious anemia who has had a gastric analysis prior to the development of the disease hydrochloric acid has been absent at this time The evidence suggests very strongly therefore that persons who develop pernicious anemia have a congenital absence of hydrochloric acid in the gastric secretions It has been established also that hydrochloric acid never returns in the gastric secretions following effective treatment of pernicious anemia even at a time when all of the gastrointestinal symptoms disappear Although an occasional case is reported in which it is claimed that hydrochloric acid was present in the stomach contents of a patient with pernicious anemia or that it appeared following treatment I have no faith in such reports and hesitate to accept them when evidence to the contrary is so overwhelming in so many thousands of patients The subject has been reviewed in the classical paper by Levine and Ladd[67] and more recently by Askey[68]

All agree that gastric analysis should always be done following the subcutaneous administration of 0 5 milligram of histamine which is a powerful stimulus to gastric secretion It has occurred occasionally that a patient has been referred to me with the statement that the diagnosis of pernicious anemia has been established by the usual findings and that an achlorhydria is present as determined by the ordinary Ewald or the alcohol test meal The reason for referring such patients usually has been a refractoriness to liver or stomach therapy A gastric analysis following the injection of histamine not infrequently has demonstrated the presence of hydrochloric acid and hence it has been established that the diagnosis of pernicious anemia was incorrect

Urine Changes and Kidney Function Tests

Over one half of the patients with pernicious anemia have a slight to moderate albuminuria and a few granular and hyaline casts in the urinary sediment These changes may be of the same nature as the albuminuria which is so commonly present in persons over 50 years of age When the anemia is severe the specific gravity is low and fixed but with a return of the blood to normal the

patients are again able to concentrate the urine to a normal specific gravity Rarely is the non protein nitrogen of the circulating blood elevated, and the phenosulfonphthalein excretion is not impaired The urea clearance is low during relapse, but it usually returns to normal during remissions at which time the blood is normal

Stools

There are no characteristic changes in the stools of patients with pernicious anemia When diarrhea is present, the stools may be light tan in color which has been attributed to an excess of stercobilin[69] In patients with severe diarrhea which complaint is uncommon in my experience, there may be an excess of mucous and pus in the feces and occasionally occult blood may be present

Examination of the stools should never be omitted in patients with the condition (1) because the ova or segments of *Diphyllobothrium latus* may be detected as a cause for the anemia which so closely resembles pernicious anemia and (2) because occult blood might be present which would suggest the possibility of gastrointestinal malignancy

It has been found by Nye[70] that there is a great increase in the number of *B Welchii* spores as compared with those in normal stools and those from a majority of patients with miscellaneous diseases It seems likely however that this increase is due to the presence of an achlorhydria per se, as it can be demonstrated in persons with this state of the gastric secretions when it is not associated with pernicious anemia

Differential Diagnosis

The diagnosis of pernicious anemia in most instances can be made with a certainty provided a sufficient opportunity is given to observe the patient and especially if it is possible to determine the effects of potent antipernicious anemia therapy In general it may be said that, if a person of middle age or older has developed recently a pronounced pallor with a definite yellowish tint, there is a possibility that the condition is one of pernicious anemia If in addition there is a histamine refractory achlorhydria and paresthesia of the hands and feet one may state positively that the likelihood of the patient having pernicious anemia is great even before the blood is examined

Other important diagnostic evidences of the disease are the attacks of recurring glossitis, about which approximately two-thirds of the patients complain, and a smooth atrophic tongue which is present in approximately one half of the patients As has been mentioned elsewhere in my experience the tongue of patients with pernicious anemia always is clean, and hence a coated tongue,

especially one which is heavily coated is strong suggestive evidence against the diagnosis

Another valuable aid in the diagnosis is the history of periods of remission in the spontaneous course of the disease One or more of these almost always occurs without reference to any known variation in diet habits or environment With the widespread use of antipernicious therapy however there is little opportunity to observe remissions unless this treatment has been stopped for some reason

There are in the blood of patients with this disorder certain characteristic changes which are almost invariably present in all cases when a definite anemia is present Hence they serve as invaluable aids in the diagnosis of the disease They are the macrocytosis the increase in the mean corpuscular volume which is always greater than 100 cubic microns leukopenia with a decrease in the percentage of neutrophils characteristic neutrophils with their multilobed nuclei poikilocytosis and anisocytosis and the striking increase in the percentage of reticulocytes following the administration of liver or desiccated stomach therapy All of these findings when considered with the various features of the history and physical examination make it possible to recognize the malady with a high degree of accuracy

The correct diagnosis is not always achieved however when a patient presents himself to a physician This is indicated by the information collected by Hardgrove and his associates[8] who found that in one half of their patients the condition was not recognized by the first physician consulted although suggestive symptoms were present Moreover in about 11 per cent of their patients the first three physicians consulted were unable to make a diagnosis It is significant as an explanation of these deficiencies in the diagnosis that about 85 per cent of their group were not studied adequately until they were hospitalized

It should be emphasized that there are a certain group of other macrocytic anemias which should be kept in mind when the diagnosis of pernicious anemia is under consideration They are the anemias associated with the following conditions *Diphyllobothrium latus* infestation various short circuiting operations and stricture of the intestines cirrhosis of the liver extensive neoplastic infiltration of the stomach as in linitis plastica sprue some cases of pellagra myxedema subleukemic leukemia various nutritional anemias in which there is a deficiency of the extrinsic factor the macrocytic anemias of pregnancy and nephritis

The details concerning the characteristics of the other types of macrocytic anemia are given in the following pages and elsewhere in this System of Medicine In general it suffices to say here that it is well to remember these facts concerning the disease pernicious anemia is always associated with a histamine refractory achlorhydria only occasionally is it present in the absence of both paresthesia of the hands and feet and recurrent glossitis the presence of an easily palpable spleen is strong evidence against the diagnosis leukopenia and poikilocytosis are

invariably associated, if the red blood cell count is 2 5 million per cubic millimeter or less, the disease almost always responds with a characteristic reticulocyte rise and increase in erythrocyte count following adequate therapy

Other Diseases Associated with Pernicious Anemia

As pernicious anemia most commonly occurs in persons of middle age or older certain other diseases which are prevalent at the time of life, are likely to be associated In my experience these should be divided into the following three groups

I Those diseases which are related etiologically to pernicious anemia The more important of these are gallbladder diseases cystitis and sometimes pyelitis, mild mental disturbances and changes in the spinal cord

II Those, which have only a fortuitous association with pernicious anemia as follows hypertension and arteriosclerosis cardiac disorders malignancy and arthritis There are of course many other conditions, which occur commonly during the years of the greatest incidence of pernicious anemia, any of which may develop simultaneously with pernicious anemia in the same patient

III There are certain disorders about which there has been some discussion as to whether they occur in some instances with greater and in others with less incidence in patients with pernicious anemia If the latter were true it would imply that this type of anemia in some unknown manner renders patients immune to various maladies and in the case of the former that it favors the development of certain other diseases

It has been reported that the following diseases occur more frequently in a patient with pernicious anemia than could be explained on a fortuitous basis cancer of the stomach angina pectoris certain skin diseases hypopituitarism thyroid disorders and diabetes On the other hand it is the belief of some students of the disease that tuberculosis occurs less frequently in patients with this type of anemia

There is no question but that gallbladder disease occurs more commonly in patients with pernicious anemia than in a comparable group as to age and sex without the disease[71] as 2 5 per cent of our patients showed evidences of gall bladder dysfunction by intravenous cholecystography

With the improvement in the methods of treating pernicious anemia it became more and more apparent that an increasing number of patients with the disease succumbed to cancer of the stomach My first impression was that as they no longer died of the anemia or its complications death resulted from such pathological conditions as this type of cancer, which were prevalent at the age at which persons are most likely to have pernicious anemia It is probable however, that the association is on a basis which is more than coincidental

The evidence indicates that gastric cancer as a sequel to pernicious anemia is not rare and gastric polyposis is much more common than in patients of a similar age group who succumb to other disorders[72, 73, 74]

Patients with pernicious anemia and angina pectoris have been reported To me it is remarkable that the association of the two conditions does not occur more frequently This is because their age incidence is approximately the same Furthermore if the present day theory of anginal pain is accepted namely that it is due to anoxia of the myocardium it is to be expected that an anemia would contribute materially to the production of anginal symptoms Studies of groups of patients with pernicious anemia show that this association is not encountered frequently For example Giffin[75] found an incidence of 2 5 per cent and Carter and Traut[76] one of 1 0 per cent in large groups of patients with this variety of anemia It is my opinion that anemia alone cannot cause the symptoms of angina pectoris It appears that there must be in addition some other factor such as a *narrowing of the coronary arteries due to arteriosclerosis or possibly in some cases an aortic insufficiency with a low diastolic pressure which results in an impaired flow through the coronary vessels Excellent reviews of the literature dealing with this topic are presented by Herrick*[77] and by Stalker[78]

It is the opinion of Witts[79] that the occurrence of pernicious anemia and hypopituitarism in the same person is more than a coincidence It is his opinion that some mechanism may be operative whereby an unidentified hormonal element leads to a degeneration of the cells of the fundus of the stomach which secrete the intrinsic factor The coexistence of the two diseases in the same patient has never been observed by me and the number of cases reported in the literature is small The burden of proof is on those who contend that the association is more than a fortuitous one

Comment has been made by Wilkinson[80] on the association of various skin diseases and pernicious anemia In his group of 370 cases there were 3 of acne rosacea 3 of psoriasis vulgaris 3 of urticaria 2 of eczema 1 of leukoplacia and 3 of pruritis vulvae This array of cases involving the skin does not seem to be an unusual number to encounter in 370 cases of any disease affecting persons of the age who are likely to develop pernicious anemia It is the belief of Wilkinson however that possibly there may be some relationship between acne psoriasis and urticaria and achlorhydria The opinion has been expressed by Murphy and Howard[81] that the incidence of vitiligo in their patients was greater than might be expected in a group of patients of similar age who did not have pernicious anemia

Although a careful study has not been made in our group of patients with pernicious anemia who now number well over 1 000 it is my impression that there is no causal relationship between diseases of the thyroid gland and this type of anemia We have observed instances of exophthalmic goiter toxic

anenoma and myxedema in patients with this variety of anemia, but the association seems to have been one merely of chance In this Stenstam[97] concurs following a comprehensive review of the literature and the study of a large group of patients A number of patients in whom pernicious anemia and fully developed myxedema have coexisted, have been reported[83], and I have observed such an association although it is rare There is no evidence of a causal relationship between the two disease states

Diabetes mellitus and pernicious anemia may be associated in the same patient, but there is no proof or suggestion that they are related etiologically In a group of 440 patients with this type of anemia, studied by Murphy and Howard[81], there were 9 patients with diabetes mellitus In Wilkinson's group[80] there were 4 patients with diabetes When the condition is present in patients with pernicious anemia it develops most frequently after 40 years of age, and consequently usually it is mild in nature

It is true that the rarity of active pulmonary tuberculosis in patients with pernicious anemia is apparent, but no one has produced convincing evidence that it is any less common in these patients, in accordance with the age and sex distribution than it is in the population at large In a group of 21 necropsies performed on our patients with pernicious anemia definite evidence of tuberculosis was found in about the same ratio as is to be expected in this age group Furthermore one patient, who was doing well as far as the anemia was concerned, succumbed to tuberculosis It must be granted, therefore, that pulmonary tuberculosis may occur in patients with pernicious anemia, and it is occasionally the cause of death in these patients Furthermore evidence at necropsy indicates that the disease is present in about equal frequency in patients with pernicious anemia as it is in the population at large This conclusion is in accord with the view expressed by Wilkinson[80]

TREATMENT

Liver Extract

The guiding principle in the treatment of patients with this disease is to administer an adequate amount of potent antipernicious anemia medication, which will cause the blood to increase to a normal level in the shortest period of time and subsequently to give a quantity which will maintain it within normal limits There is general agreement that this is accomplished with the most efficiency and certainty by the intramuscular injection of liver extract which should always be U S P liver extract preparations, certified for potency in terms of arbitrarily defined units The accepted definition of a unit is the daily quantity

of material necessary to produce a maximum reticulocyte rise and a satisfactory increase in erythrocytes

Preparations of liver extract are available in strengths of 1, 2 2 5 3 3 4 5 10 and 15 units per cubic centimeter Some have claimed advantages for the crude or more dilute preparations especially in the treatment of patients with subacute combined degeneration of the spinal cord but in my opinion there is no convincing evidence to indicate that these are superior in any way to the preparations containing 10 to 15 units per cubic centimeter Furthermore, as the latter are more concentrated they are more satisfactory to administer intramuscularly While it is possible to inject certain preparations intravenously such a route of administration has no particular advantages and disturbing reactions may result

In summary it may be said that the intramuscular treatment with liver extract is preferred because the maximum results are attained moreover a certain number of patients in relapse will respond to intramuscular injections after failure of oral preparations to produce satisfactory results and of greatest importance the neural manifestations are affected more favorably

In the treatment of patients during the period of relapse it is always advisable to err on the side of administering an excess of liver extract rather than to give a suboptimal amount In relapse therefore it is recommended that one should inject 1 c c daily containing 15 units for the first week of treatment Following this 1 c c of the same potency of liver extract should be administered three times a week until the blood reaches 5 0 million per cubic millimeter in the case of men and 4 5 millions in women In addition the cell size should be brought to normal, 86 to 96 cubic microns the color index should be 1 0 and the mean corpuscular hemoglobin concentration should be 30 to 33 per cent It has never been my experience that even a gross overdosage produced harmful effects or an excessively high red blood cell count such as is seen in polycythemia

After the red blood cell count has reached normal limits it should be impressed upon the patient that it will be necessary to continue with some form of antipernicious anemia medication at regular intervals for an indefinite period of time regardless of a disappearance of all symptoms and the presence of a normal sense of well being The precise amount of liver extract which is necessary to maintain the blood within normal limits varies with different individual but the matter is so important that not the slightest risk of a suboptimal dosage should be taken I prefer to give 1 c c intramuscularly containing 15 units at weekly intervals or 2 0 c c containing 30 units at biweekly intervals although some recommend that the interval between doses be lengthened to 3 or 4 weeks

It is imperative, however to maintain the blood at a high level of normal and hence it is wise in planning the maintenance dose to give an excess rather than an amount which is insufficient To those of us who employed the liver

treatment, when it was first introduced in 1926, it is now clear that we were too content to give an amount which controlled the symptoms of anemia, despite the fact that the red blood cell count was often in the vicinity of 3 8 or 4 0 millions per cubic millimeter

I am in accord with the recommendations of Strauss, Solomon and Fox[84] in regard to the maintenance dose of liver extract which are as follows (1) the red blood cell count should be 4 5 million per cubic millimeter or higher, and the mean corpuscular volume within normal limits, (2) there must be no symptoms of any nature attributable to pernicious anemia such as glossitis or indigestion (3) and the most important of all, if there is any recurrence of numbness and tingling or other paresthesia of the extremities the dose of liver extract should be doubled, (4) if the patients present any other manifestations which might be interpreted as due to a progression of the spinal cord lesions this is also an indication to double the dose immediately, (5) finally, if the patient should develop any type of infection, even a common "cold", then also the dose should be doubled An additional precaution to keep in mind is that elderly patients in general require at least 50 to 100 per cent more therapy than do patients under 55 years of age

By some it is considered convenient to give the initial treatment in the form of a single massive dose, the so-called "depot treatment" of the Germans It has been suggested by Askey[85] that 1 c c containing 15 units be given on one day and on the following day, if there has been no untoward reaction, an additional 9 c c containing 135 units may be given intramuscularly Thereafter, it is recommended that 2 c c or 30 units be given each month Although the massive dose method has certain advantages, the results attained generally are not as good as those which follow the injection of comparable amounts of liver in small regular, intermittent doses[86] When large amounts of liver are given in a single dose they do spare the patient the inconvenience of more frequent injections, but most important of all in patients who are undependable with respect to taking regular therapy it insures that they will derive the benefit from a considerable quantity of potent material for a long time

It has been demonstrated conclusively that folic acid when given intravenously intramuscularly or orally in appropriate doses, will exert a favorable effect on the blood of patients with certain types of macrocytic anemia This has been observed in patients with pernicious anemia, nutritional anemia sprue, the macrocytic anemia of infancy and of pregnancy and the macrocytic anemia associated with total gastrectomy This subject has been reviewed recently by Spies and also by Berry[86( ) 88(b)] Folic acid produces the usual rise in reticulocytes in the circulating blood, the increase in erythrocytes similar to that observed following liver therapy and obvious evidence of remarkable general improvement in the patient s sense of well being Those who have had the most

extensive experience with the drug however believe that additional observations extending over a longer period are necessary in order to evaluate accurately the anti pernicious anemia activity of the material Furthermore there is some suggestive evidence to indicate that it may not be as effective as liver extract in the control of the neurological manifestations Additional observations are needed also to evaluate this possibility

The optimum dose has not been determined One of my patients with pernicious anemia responded satisfactorily to the oral administration of 5 milligrams daily It is always advisable however to err on the safe side in treating patients with pernicious anemia A satisfactory daily dosage either intramuscularly or orally in my opinion is 20 milligrams

The Effects of Treatment — The immediate effects of liver therapy in a patient with pernicious anemia who has a severe anemia are among the most dramatic witnessed in the entire field of medicine When the preparation is given intramuscularly obvious and striking evidences of improvement become apparent within 36 to 72 hours The appetite which often has been completely lacking not infrequently becomes excellent and in some instances even ravenous With this there is regularly an abatement of the constantly present gastrointestinal complaints unless some complication such as cholecystitis is present The body temperature falls to normal as does the pulse rate and there is a remarkably rapid gain in strength Unless the patient is handicapped by irreparable damage to the nervous system there is a return to a normal or reasonably normal existence within the next 6 to 12 weeks

It is to be expected that the manifestations due to involvement of the nervous system will require longer to improve and in some instances they may remain unchanged If the proper treatment is given however at least there should not be a progression of these lesions A fuller discussion of this phase of the treatment will be given under the heading of Prognosis

Changes in the Blood Following Treatment — The earliest evidence of a remission in the circulating blood is an increase in the young red blood cells or reticulocytes which usually begins within 36 to 48 hours after parenteral liver therapy has been instituted and within 3 to 6 days after oral therapy Ordinarily the reticulocytes of the peripheral blood number 1 0 per cent or less and this is also true of the blood of patients with pernicious anemia in relapse Coincident with the evidences of clinical improvement these young cells begin to increase in numbers and usually reach their maximum percentage on the 5th to the 7th day when parenteral therapy is used and on the 7th to the 9th day with oral therapy The curve of the reticulocytes usually returns to normal on the 10th to the 15th day after treatment has been initiated The typical reticulocyte response in a patient with pernicious anemia who has received intramuscular injections is shown in Fig 1

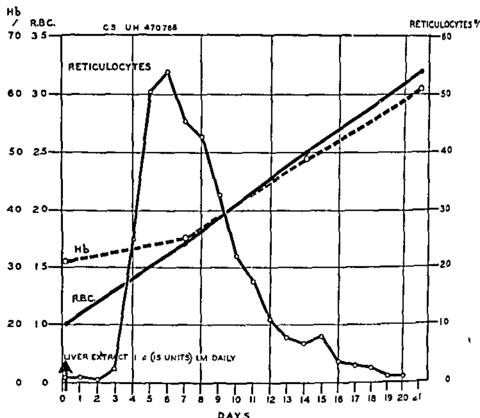


FIG 1 The hemoglobin is expressed in percentage with 15 6 Gms equalling 100 per cent the red blood cell count in millions per cubic millimeter and the reticulocytes in percentage The chart shows the effects of the daily intramuscular injection of 15 units of potent liver extract in a patient with pernicious anemia during relapse The earliest evidence of response to treatment is shown on the third day when there is a beginning rise in the percentage of reticulocytes the maximum number being attained on the 6th day when it reaches 54 per cent The curve then gradually falls until the percentage of these cells becomes approximately normal on the 16th day Associated with this reticulocyte response there is an increase in the number of red blood cells at the rate of 800 000 per cubic millimeter per week and a gain in hemoglobin of 10 per cent per week

The peak of the reticulocyte curve indicating the maximum number of these cells which are in the blood following efficient treatment bears an inverse relationship to the level of the red blood cell count prior to therapy As the maximum height of the reticulocyte curve varies with the type and hence the potency of the antipernicious anemia medication administered, it is utilized to assay various stomach and liver preparations which are used in the treatment of pernicious anemia Table II shows the maximum reticulocyte responses in patients with pernicious anemia following the administration of different types of liver and stomach therapy

TABLE II

Red Blood Cell Count Before Treatment	Ventriculin 40 Gm Daily	Liver Extract Oral 1½ Units Daily 18 (Gm)	Liver Extract Intramuscularly 1-2 Units Daily
Millions Per Cu Mm	Reticulocytes %	Reticulocytes %	Reticulocytes %
0 5	61 2	55 7	56 8
1 0	41 0	34 6	40 0
1 5	28 4	22 3	28 0
2 0	18 6	14 1	19 0
2 5	11 1	8 4	12 0
3 0	5 1	4 1	6 4
3 5	0 3	0 9	1 8

The anticipated maximum reticulocyte percentage following different types of antipernicious anemia therapy with various initial pre treatment red blood cell counts is shown above For example if a patient with pernicious anemia has a red blood cell count of 1 0 million per cubic millimeter immediately before treatment and is given ventriculin in the dosage indicated above it is anticipated that the peak of the reticulocyte respons would be approximately 41 8 per cent on the 6th to the 7th day If oral liver extract is given the peak would be about 34 6 per cent and if intramuscular liver extract is administered the peak would be in the vicinity of 40 0 per cent With the parenteral type of therapy the peak often is reached sooner than when oral medication is given that is within 5 or 6 days

The optimum response of the erythrocytes to effective therapy has been determined by the study of the blood of many patients who have been treated both with liver and with stomach therapy The red blood cells usually increase at a rate of 250 000 to 350 000 per cubic millimeter per week and in some instances the gain is slightly greater This continues until the red blood cell count is normal This statement has exceptions for various complications may inhibit the response to a certain extent This occurs if an infection of any type is present if the medication is not of full potency or the dose which is administered is too small if the patient is elderly or if some unusual complication such as bleeding is present In a study of the effects of treatment with liver extract on 523 of our patients with pernicious anemia Riddle[87] found that the average weekly increase in the erythrocyte count at the end of 2 weeks of treatment had an inverse relationship to the red blood cell count before treatment This relationship can be expressed in the equation $I = 0.78 - 0.174\ Eo$ where I is the average weekly increase in the erythrocyte count after two weeks of treatment and Eo the erythrocyte count before therapy expressed as millions per cubic millimeter

Allergy to Parenteral Injections of Liver — In a relatively small group of patients which I would estimate at about 5 per cent after parenteral

liver extract has been given continuously for a long time or discontinued and then resumed allergic manifestations may become apparent. The symptoms are variable in intensity from those which would be considered as minor annoyances to the rare severe reactions characterized by loss of consciousness and incontinence. The common symptoms are flushing of the face, palpitation and tachycardia, itching of the skin, urticaria, "stuffiness" of the nasal passages and less frequently, outspoken asthmatic attacks. These manifestations usually appear within a few minutes following the injection of the liver extract and generally can be relieved or prevented by the subcutaneous administration of from 0.3 c.c. to 0.5 c.c. of a 1–1,000 solution of epinephrine hydrochloride.

Usually when the reactions appear, it is necessary to alter the method of treating the pernicious anemia. This is because the acquired allergy is an organ sensitivity rather than a species type and hence it would do no good to change to a liver extract made from beef liver, if the patient were sensitive to swine liver, because the same reaction would be produced. In other words if a patient is sensitive to liver extract, it is a sensitivity to the antipernicious anemia liver extract made from the livers of all animals. The most comprehensive article dealing with this subject is the one by Kaufman, Farmer and Reich[88] in which a review of thirty five articles is given as well as a consideration of their own 11 cases.

The management of patients who develop sensitivity to liver extract should be as follows: first, oral preparations might be employed, as usually they can be taken with impunity or, what is more satisfactory the patient should be desensitized to liver extract. Oral ventriculin, liver extract or "extralin" might be used and reference should be made to the section dealing with oral antipernicious anemia therapy for details of how these forms of treatment should be administered.

If the patient is to be desensitized, the following plan is suggested: 0.1 c.c. of a 1–10 dilution of liver extract is given subcutaneously, and this dose is increased about 0.2 to 0.3 c.c. every second or third day for 2 or 3 weeks until the patient is receiving the full therapeutic dose of concentrated liver extract containing 15 units per c.c. It should be kept in mind that during the process of desensitization the patient may experience symptoms but these can be relieved promptly by the subcutaneous injection of epinephrine. Once the desensitization has been accomplished, it is probably of some importance to keep the patient in this state and hence the maintenance dose should be smaller and should be given at more frequent intervals for example, 0.5 c.c. may be given every 10 days or once weekly.

If folic acid proves to be an effective therapeutic agent, its use in patients with pernicious anemia who become sensitized to liver extract may be the most satisfactory solution of that difficulty.

Oral Preparations

Although it is readily conceded that the oral preparations are less effective than the intramuscular injection of liver extract in the treatment of pernicious anemia nevertheless it is advisable sometimes to give them and hence the fact that effective treatment by this method is feasible should be kept in mind

When the liver treatment was first introduced by Minot and Murphy in 1926 it was recommended that raw or cooked liver be given in the amount of one half pound daily until the blood reached normal and then a variable amount of liver usually one fourth pound be given daily or 5 times a week as a maintenance dose Although I still have under my observation one patient who has maintained his blood in a normal state for 18 years with cooked liver taken as one fourth pound 5 times a week it is by his choice rather than my prescription and with my amazement that he can consume this quantity over such a long period It is usually not possible for the average patient with pernicious anemia to continue with this form of treatment for many months

At present liver extract powder for oral use is available and may be used in the treatment of patients with the disease It should be given dissolved in water tomato juice or orange juice in doses of 12 75 grams (a level tablespoonful) 3 times daily which represents one official unit Another form of antipernicious anemia medication which may be used effectively is extralin It is a combination liver stomach preparation and probably is the best of the oral types of medication It should be given in maintenance doses of 2 grams 4 pulvules 3 times daily Ventriculin or desiccated defatted hog stomach is effective in the treatment of pernicious anemia provided only certified products are used This material should be administered suspended in water or tomato juice in a dosage of 40 grams daily until the blood reaches normal then in amounts varying from 20 to 30 grams daily in order to maintain the blood at a normal level

It has been reported recently by Spies and his associates[46] that synthetic folic acid administered orally intramuscularly or intravenously is effective in treating the macrocytic anemia of pernicious anemia pellagra sprue various other nutritional states and pregnancy In a more recent article following a study of 27 patients with a macrocytic anemia due to various causes this work is confirmed by the same investigator[47] From the data presented in the latter article there is no question that the administration of synthetic folic acid in amounts varying from 20 to 200 milligrams daily either parenterally or orally will produce a reticulocyte rise and an increase in the red blood cell count and hemoglobin content of the peripheral blood in a manner similar to highly potent liver extract or ventriculin Furthermore the patients experienced all of the subjective and objective signs of improvement which are noted following the exhibition of other potent antipernicious anemia preparations It has been found that the

administration of as much as 400 milligrams of folic acid daily will not cause any untoward symptoms but that a daily dose of from 5 to 10 milligrams parenterally or in some patients 10 milligrams daily by mouth often will evoke a maximum hematological response While the minimal effective dosage and the amount necessary to maintain the blood in a normal condition are not known, nor is there data which have a bearing on the effect of this therapeutic agent on combined system disease, the evidence at present strongly suggests that in the future folic acid may be used widely in the treatment of the macrocytic anemias of pernicious anemia sprue pellagra, other nutritional anemias and pregnancy If it proves to be highly effective its use is suggested at once in all patients with such anemias and especially in those who become sensitized to liver extract

Other Forms of Therapy Than Specific Antipernicious Anemia Therapeutic Agents

Bed Rest and Physiotherapy — Patients with a red blood cell count of less than 2 0 million per cubic millimeter should be confined to bed but urged to be up in a chair for short intervals and even to walk around as soon as the blood begins to show material improvement Their activity should be increased gradually depending largely on their subjective sensations of fatigue as a method of controlling the extent of their exercise and rest In the past probably there has been a tendency to limit the activities of these patients too rigidly

In patients especially with changes in the spinal cord which have produced varying degrees of spastic paraplegia and ataxia both passive and active exercises and massage are indicated Occupational therapy hydrotherapy and local applications of heat are useful also

Diet — No special attention need be given to the patient's diet except to provide an abundant supply of food of all types in order to appease the appetite which usually is stimulated, sometimes to huge proportions by the ant pernicious anemia medication Care hould be taken to see that ample protein is ingested in the form of meat eggs and milk to the amount of 1 5 grams per kilo per day This is useful as it provides an adequate amount of the extrinsic factor which is known to be present in these forms of protein It is not necessary for the patient to ingest cooked li er in the diet but it is a good form of food and if not disliked should be taken in the amount of at least one half pound per week

If the patient partakes of an abundant diet, there is no indication to add additional vitamins to the food intake Some claim however especially when advanced spinal cord lesions are present that vitamin therapy makes improvement more certain and the results more complete There can be no harm in the oral administration of powdered yeast in doses of 15 to 20 grams 2 or 3 times daily which should be ample to satisfy all of the vitamin B requirements

Hydrochloric Acid — Although it is known that all patients with pernicious

anemia have achlorhydria there is no convincing evidence that the therapeutic administration of dilute hydrochloric acid is useful or necessary for the control of the gastrointestinal symptoms of this type of anemia or that it exerts a beneficial effect on any phase of the disease In the first place it is not possible by oral medication to supply the amount of hydrochloric acid which is present normally in the gastric secretions For example it has been stated by Koehler and Windsor[89] that the amount secreted by the stomach following an average meal is in excess of 10.4 c c of normal hydrochloric acid and that 35 c c (7 teaspoonfuls) of U S P dilute hydrochloric acid is required to bring the gastric contents to the normal post meal physiological level with a pH of from 1 6 to 1 8 It should be remembered also that patients with pernicious anemia probably have had an achlorhydria since birth and despite this for a very great portion of their lives they have been entirely free from all gastrointestinal symptoms

Usually in almost all patients who are treated effectively with antipernicious anemia medication the gastrointestinal symptoms disappear promptly If they do not then one should suspect that the patient is suffering from cholecystitis with or without stone with secondary involvement of the gastrointestinal tract from the nervous system or from some other conditions such as a spastic bowel

Regardless of the nature of the residual abdominal complaints hydrochloric acid therapy may be given a trial for it certainly can do no harm to administer it in doses of 1 teaspoonful of the dilute U S P preparation in a full glass of water sipped with meals

Iron —Ordinarily it is not necessary to administer this metal to patients with pernicious anemia because there is no deficiency of it in the body in fact there may be an excess If there is an undue delay in the regeneration of hemoglobin and hence a persistence of a low color index or of a mean corpuscular hemoglobin concentration below 30 per cent then iron should be given in the form of ferrous sulfate 0 3 gram 3 times daily after meals Rarely has this type of medication been necessary in my experience and there is no possible excuse for its routine administration to all patients with this type of anemia

Blood Transfusions —It is a wise precaution in all patients with pernicious anemia who have a red blood cell count of 1 0 millions per cubic millimeter or less to determine their blood type and make all necessary arrangements for a blood transfusion promptly if the indications become apparent This is to make certain that the patient does not succumb before the beneficial and life saving effects of the antipernicious anemia medication have time to become effective Otherwise in my experience except in the presence of a severe infection which may inhibit the effect of liver extract there are no indications for blood transfusions in this disease

Care of the Bladder —Often of immediate importance when the patient is first seen is the inability of the patient to void urine due to neural changes

administration of as much as 400 milligrams of folic acid daily will not cause any untoward symptoms, but that a daily dose of from 5 to 10 milligrams parenterally or in some patients 10 milligrams daily by mouth often will evoke a maximum hematological response While the minimal effective dosage and the amount necessary to maintain the blood in a normal condition are not known, nor is there data which have a bearing on the effect of this therapeutic agent on combined system disease, the evidence at present strongly suggests that in the future folic acid may be used widely in the treatment of the macrocytic anemias of pernicious anemia sprue, pellagra other nutritional anemias and pregnancy If it proves to be highly effective its use is suggested at once in all patients with such anemias and especially in those who become sensitized to liver extract

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not coöperate fully This is chiefly because with treatment the symptoms subside and when complaints are absent it is a natural impulse to defer treatment until they reappear Unfortunately the manifestations of anemia are not present or are negligible even when the red blood cell count is slightly below normal that is between 3 8 and 4 0 millions per cubic millimeter At this level however it is known that there may be a progression of the spinal cord changes until they arrive at a point when improvement is impossible At this stage the patient develops a spinal cord bladder with a residual urine a cystitis and an ascending infection of the urinary tract with abscesses of the kidneys and death from septicemia The infection also always exerts an unfavorable influence on the liver therapy rendering it less effective Hence when these circumstances prevail often it is not possible to maintain the blood at a normal level despite intensive treatment

In general it may be said that when a patient with pernicious anemia is observed for the first time it is impossible to state precisely the anticipated length of life that is before him or what will be the cause of death In the period before liver therapy it could be said that the average length of life of such patients was between 2 and 3 years In some instances however there was a remarkable exception to this rule because for some unknown reason a patient with the disease experienced a remission of variable length occasionally as long as 10 years or more In the average case however the period of remission was short lived persisting for about 3 to 6 months and although most of the symptoms abated the blood usually did not rise to above 3 5 millions per cubic millimeter In one instance I observed a patient who almost succumbed to the disease but was sustained as the result of many blood transfusions At about the time it was thought that death was impending he developed a spontaneous remission and made an apparent recovery which persisted for about 10 years He then had a complete relapse but fortunately by this time liver therapy had been introduced and he has been treated successfully ever since

Experience with the modern treatment during the past 19 years has led me to the following conclusions concerning the results which may be expected in regard to the prognosis

1 A patient with pernicious anemia has an equal chance of dying from this disease or some entirely unrelated condition

2 If death does occur from pernicious anemia it is probable that it will not be due to the anemia but it will almost surely result from complications incident to the degenerative changes in the nervous system

3 There is some suggestive but not conclusive evidence to indicate that although a patient may live to an advanced age as the result of treatment he has less chance of attaining his normal life span based on his normal life expectancy at the time of the onset of the disease

which affect the normal control of the sphincters of the bladder It is advisable in many cases to introduce an inlying catheter, when a residual urine is present although the Credé method of manual emptying should be employed first If there has been difficulty in voiding for some time, usually there is stasis of urine in the bladder and an associated urinary infection This is of major importance because such an infection materially affects unfavorably the response to liver therapy and it may not be possible to control the anemia satisfactorily until the infection is eliminated

The cystitis may be treated by bladder irrigations of 0 25 per cent acetic acid introduced every 2 to 4 hours In addition either sulfadiazine, in doses of 0 5 gram 4 times daily or penicillin in full doses of 20 000 every 3 hours day and night may be tried It is too early to make any statement about the control of urinary infections by streptomycin, but the preliminary reports indicate that this form of therapy may be effective in the types of infecting organisms which resist other forms of therapy

Prognosis and Course of the Disease

Before the introduction of liver therapy in 1926 the outlook for patients with pernicious anemia was hopeless as the disease terminated fatally with few exceptions within a period of 2 to 3 years It is true, as Evans[27] emphasized just before the introduction of the modern treatment of the disease, that no patient with pernicious anemia had ever been cured, nor was any treatment available with the possible exception of blood transfusions which could prolong life even for brief periods The latter, at the most, produced only transient improvement

This then represented accurately the gloomy outlook for these patients before the modern treatment was available In the 19 years that this form of therapy has been given a thorough trial certain definite conclusions have become apparent In the first place from a theoretical standpoint it should be possible *for a patient with uncomplicated pernicious anemia to live out* his normal span of life provided the proper treatment was prescribed and followed and if irreparable damage had not been done to the nervous system

As determined by observation however most patients do not survive for the normal span of life, mainly for two reasons One which is unavoidable is that they succumb to fortuitously associated diseases which are commonly the cause of death in this age group They are chiefly heart disease cancer, especially of the stomach pneumonia and other diseases which are recognized as common causes of death at middle age or older The second reason which is more important because at least theoretically it is preventable is that the patients in some cases are not treated properly that is the medication is not given in accordance with the most generally accepted views, and furthermore many patients do

not cooperate fully This is chiefly because with treatment the symptoms subside and when complaints are absent it is a natural impulse to defer treatment until they reappear Unfortunately the manifestations of anemia are not present or are negligible even when the red blood cell count is slightly below normal that is between 3 8 and 4 0 millions per cubic millimeter At this level however it is known that there may be a progression of the spinal cord changes until they arrive at a point when improvement is impossible At this stage the patient develops a spinal cord bladder with a residual urine a cystitis and an ascending infection of the urinary tract with abscesses of the kidneys and death from septicemia The infection also always exerts an unfavorable influence on the liver therapy rendering it less effective Hence when these circumstances prevail often it is not possible to maintain the blood at a normal level despite intensive treatment

In general it may be said that when a patient with pernicious anemia is observed for the first time it is impossible to state precisely the anticipated length of life that is before him or what will be the cause of death In the period before liver therapy it could be said that the average length of life of such patients was between 2 and 3 years In some instances however there was a remarkable exception to this rule because for some unknown reason a patient with the disease experienced a remission of variable length occasionally as long as 10 years or more In the average case however the period of remission was short lived persisting for about 3 to 6 months and although most of the symptoms abated the blood usually did not rise to above 3 5 millions per cubic millimeter In one instance I observed a patient who almost succumbed to the disease but was sustained as the result of many blood transfusions At about the time it was thought that death was impending he developed a spontaneous remission and made an apparent recovery which persisted for about 10 years He then had a complete relapse but fortunately by this time liver therapy had been introduced and he has been treated successfully ever since

Experience with the modern treatment during the past 19 years has led me to the following conclusions concerning the results which may be expected in regard to the prognosis

1 A patient with pernicious anemia has an equal chance of dying from this disease or some entirely unrelated condition

2 If death does occur from pernicious anemia it is probable that it will not be due to the anemia but it will almost surely result from complications incident to the degenerative changes in the nervous system

3 There is some suggestive but not conclusive evidence to indicate that although a patient may live to an advanced age as the result of treatment he has less chance of attaining his normal life span based on his normal life expectancy at the time of the onset of the disease

4 If death is not due to the neurological manifestations of pernicious anemia probably it will be from some entirely unrelated condition such as heart dis ase, cancer, apoplexy pneumonia or nephritis

5 It is undoubtedly true that in those patients who eventually succumb to pernicious anemia the prognosis for the duration of life is directly related to the extent and duration of the involvement of the nervous system It is likely that the duration of neurological involvement is of more importance from this stand point than is the extent of the neurological lesions although both should be taken into consideration It is the belief of Hyland and Farquharson[90] that no im provement resulted in the neurological involvement in their patients if the changes had been present for a period of 4 years or longer I am in accord with this statement but believe that it is more accurate to state that symptoms which have been present for as long as 2 years, are very unlikely to respond favorably

In evaluating the prognosis in any given case with the nervous manifestations however, the extent of the involvement must also be taken into account It is my experience as it is of others[90], that the evidences of changes in the nervous system showing the best response to treatment are the parathesias disturbances of joint sense and gait, impairment of superficial sensation and sphincter control There is frequently a gratifying tendency to recover from psychic disturbances Those signs, which seem to be the most refractory to the treatment are the diminished vibratory sense the Babinski reflex and the absence and diminution of the Achilles reflex In general it may be said that those with parathesia and evidences of lesions of the posterior columns have a more favorable outlook and those with combined degeneration of the cord and presence of a residual urine in the bladder with a concomitant cystitis or more extensive involvement of the urinary tract usually survive the shortest period of time

These conclusions are based on the effect of treatment from the time liver therapy was introduced in 19 6 If only the patients who had been treated during the past 8 to 10 years were considered the results undoubtedly would be better This is because during this period the main form of treatment has been with liver extract intramuscularly, and superior results have been attained Also during this interval it has been more generally appreciated that it is necessary to maintain the blood at a high level of normal rather than at a point where the symptoms of anemia are not present

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA, DUE TO VARIOUS CAUSES

MACROCYTIC ANEMIA DUE TO A DEFICIENCY OF THE EXTRINSIC FACTOR (EXOGENOUS PERNICIOUS ANEMIA)

If one accepts Castle's theory that the extrinsic factor in the diet unites with the intrinsic factor in the gastric secretions to form the erythrocyte maturing factor then from a theoretical standpoint at least it must be considered that a macrocytic anemia will result from a deficiency of the extrinsic as well as the intrinsic factor In my opinion this undoubtedly does occur and furthermore in perhaps one third of the patients with pernicious anemia a deficiency of the extrinsic as well as of the intrinsic factor is of some importance from the stand point of the cause of the anemia I say this mainly because it is known that if Brewer's yeast in sufficient amounts is given a hematological remission will result[91] in about one third of the patients with pernicious anemia

A macrocytic anemia in which the changes in the blood resemble in all respects those seen in true Addisonian pernicious anemia undoubtedly does occur in patien with a deficiency of the extrinsic factor Such cases have been reported by Groen and Snapper[92] and Alsted[93] The latter observed a patient who had subsisted on an abnormal diet for a period of 7 years which was de ficient in meat eggs and milk These are regarded by Alsted as the chief sources of the extrinsic factor A complete remission in the severe macrocytic anemia including a reticulocyte response followed treatment with nothing except ex trinsic factor continued in an abundant diet It is the opinion of Alsted that exogenous pernicious anemia occurs more frequently than is generally believed, but that its presence is obscured because both stomach and liver preparations are equally effective in the exogenous and endogenous forms

The following patient whom I observed undoubtedly had a macrocytic anemia associated with a diet obviously deficient in meat eggs and milk and hence it may be concluded one lacking in the extrinsic factor He was a 24 year old male who had a red blood cell count of 1 7 millions per cubic millimeter and a hemoglobin percentage of 38 per cent (6 0 grams) The leukocyte count was 2 700 per cubic millimeter the mean corpuscular volume 135 cubic microns and the mean corpuscular hemoglobin concentration 26 per cent Sternal puncture showed the characteristic findings of a megalocytic anemia with active erythropoiesis and many large megaloblasts some in mitosis Free hydrochloric acid was present in the gastric secretions He gave the remarkable dietary history that since childhood he had subsisted on a diet consisting mainly of coffee and doughnuts with a negligible amount of milk daily The only explanation obtainable for such a strange food intake was that he had been unable to eat

regular food" Attempts to treat him solely with an adequate diet during the state of the severe anemia were interrupted because his condition became rapidly worse, and hence he was given intramuscular liver extract This produced a rise in the reticulocytes and an increase in the erythrocyte count to normal within a few weeks He has now been induced to partake of a normal diet and has remained in good health with no additional form of therapy, for a period of almost 2 years

In concluding that a deficiency of the extrinsic factor is the cause of a macrocytic anemia in any given patient ideally it should be demonstrated that, (1) the patient has partaken of a diet which is deficient in milk, eggs and meat over a long period of time, (2) that the intrinsic factor is present (this is not ordinarily feasible on account of the difficult technic, (3) that the liver is not damaged extensively as indicated by normal liver function tests (4) that an 80 per cent alcoholic extract of beef muscle, which is practically free from protein but known to contain the extrinsic factor, can produce a reticulocyte rise and an increase in the red blood cell count when added to the diet, (5) that it is possible for the patient to remain in good health with no other treatment than a normal diet, (6) that no other condition is present such as intestinal strictures or other abnormalities which might be responsible for the macrocytic anemia

It is appreciated, of course, that the conditions given above cannot be fulfilled always Hence it is admittedly most difficult to establish beyond the question of a doubt that a deficiency of the extrinsic factor is partially responsible for a macrocytic anemia or is the sole cause of it On the other hand it seems safe to say that presumptive evidence of such an anemia is not difficult to obtain and it is likely that a deficiency of the extrinsic factor is active in producing such an anemia in occasional cases and acts as a contributory factor in some cases of true pernicious anemia

Tropical Macrocytic Anemia

In 1930 Lucy Wills[94] described this type of anemia as occurring in pregnant women in India The blood and bone marrow findings were identical with those of pernicious anemia and it responded at least to crude liver extract preparations although it is said to have been *refractory to the more refined* products It differs from true pernicious anemia, however in that the amount of hydrochloric acid in the gastric secretions usually is normal, there is no increase in the plasma bilirubin, the nervous system is not involved, and a satisfactory therapeutic response follows the administration of yeast autolyzed yeast and liver It is the uniformly beneficial effect of yeast which suggests that this variety of anemia is due to a deficiency of the extrinsic factor Although the disease was first described as occurring in the pregnant state, it is also observed in non pregnant women and in males

Recently Watson and Castle[95] have emphasized the work of previous investigators who have reported that certain macrocytic anemias of the tropics usually associated with pregnancy fail to respond to liver extract administered parenterally but react with rapid blood regeneration following the oral administration of liver extract liver or autolyzed yeast They reported a macrocytic anemia in 3 women 2 of whom were pregnant and in whom there was a striking dietary deficiency in which there was a therapeutic failure of potent liver extract when it was given parenterally In all 3 of these cases there was a response to oral liver extract These observations according to Watson and Castle suggest two matters of importance (1) that a therapeutic trial of orally administered liver extract is desirable in patients with macrocytic anemias especially in pregnancy when they are refractory to parenterally administered liver extract and (2) that possibly the digestive organs in this type of patient form a new hematopoietic substance from liver extract in a manner analogous to the food gastric factor relationship in Addisonian pernicious anemia

Macrocytic Anemia in Liver Disease

It was pointed out by Wintrobe in 1933[96] that a macrocytic anemia occurred in about 33 per cent of a large group of patients with liver disease A year later Goldhamer and his associates[97] threw further light on the relation of the liver to macrocytic anemia by studying the potency of extracts prepared from the livers of patients dead from various disorders They found that the antipernicious anemia principle was absent from the liver of a patient with pernicious anemia who had been inadequately treated but that it was present in patients with this disease who had received sufficient treatment Furthermore it was found to be absent from the liver of a patient with cirrhosis of the liver, and that a macrocytic anemia closely resembling that of true pernicious anemia may be present in such a patient The assumption is therefore that in a condition such as cirrhosis producing widespread liver damage there is an inability of the liver to store the active principle and present it to the bone marrow for utilization in the proper form

The blood picture in hepatic disease may simulate that of pernicious anemia but often the conditions may be differentiated readily because free acid is present in the patient s gastric secretions and the bromsulfalein test for liver function should indicate definite impairment Furthermore rarely are there changes associated with lesions in the nervous system The anemia in patients with cirrhosis may be augmented also by a deficient food intake as these patients often are heavily alcoholic and hence partake of a poorly balanced diet which often may be lacking in the extrinsic factor Certainly in any case of macrocytic anemia in which free hydrochloric acid is present in the gastric secretions and

there is an absence of acroparathesia and other signs of neurological involvement one should always consider the possibility that the patient may be suffering from extensive involvement of the liver which most commonly is cirrhosis

Macrocytic Anemia Associated with Intestinal Strictures and Anastomoses

Since Faber first reported a case in 1897[98] of stricture of the intestine associated with the blood picture of pernicious anemia, it has been known that various intestinal lesions may be responsible for the typical changes in the blood of a macrocytic anemia The pathological picture is either a stricture of the colon or small intestine, usually the ileum, or an enteroenterostomy or enterocolostomy opening, a gastrojunocolic fistula or a gastrocolic fistula In about one half of the cases, when the lesion is in the small intestine it is due to tuberculosis In the remainder of the small intestinal lesions it is attributed to nonspecific terminal ileitis The anastomoses are most commonly an enteroenterostomy or enterocolostomy performed for the relief of intestinal obstruction

The anemia which is present with intestinal lesions, is almost always of the macrocytic type, resembling true pernicious anemia with a mean corpuscular volume of 110 to 120 cubic microns or greater In approximately one half of the cases reported in the literature there is free hydrochloric acid in the gastric secretions which sharply differentiates the condition from pernicious anemia It has been reported by Barker and Hummel[99] that the intrinsic factor of Castle has been detected in 1 of the 2 cases in which this has been investigated In 2 additional cases the response to a diet rich in extrinsic factor was interpreted as indicating that the intrinsic factor was present

The cause of the anemia due to lesions of the intestines is not clear It is possibly true that failure to absorb the antipernicious anemia factor plays a role in this respect It should be noted however as Barker and Hummel[99] point out that a study of the absorption of dextrose fat and ascorbic acid does not bear out the assumption that deficient absorption alone accounts for the condition These observers make the suggestion that as a result of the lesions there may be excessive bacterial activity in the gastrointestinal tract which may prevent the formation or destroy the hematopoietic factor, or by this action elaborate excessive amount of the toxic products of bacterial putrefaction' which cannot be detoxified by the body

Experience has shown that without surgical or antipernicious anemia therapy the outlook for improvement is poor Any operative procedure to correct the condition is associated with a high mortality rate and elimination of the intestinal abnormality may or may not be followed by a cure There is less likely to be success following an anastomotic operation designed to circumvent a stricture

than there is with resection of the stricture or restoration of the normal continuity of the bowel when an anastomosis is the lesion Experience has shown that the best success follows in patients with strictures and in young patients with anastomoses Although liver therapy may control the anemia it cannot be expected to relieve the symptoms of partial intestinal obstruction This type of treatment alone however is to be recommended for older patients with well functioning anastomoses in whom the operative risk is considerable

ACHRESTIC ANEMIA

The term achrestic anemia was introduced by Wilkinson and Israels[100] in 1935 to describe a group of cases which closely resembled pernicious anemia in many respects but differed from it sharply in certain others as follows (1) free hydrochloric acid may be present in the gastric secretions (2) there is a failure to respond satisfactorily to antipernicious medication and (3) it may be demonstrated that the antianemic factor erythrocyte maturing factor is present in the liver This latter finding would indicate that the extrinsic and intrinsic factors are intact and that they have interacted to form the erythrocyte maturing factor which is stored in the liver If these observations are verified the only assumption which can be made concerning the essential cause of the anemia is that there is a failure of the bone marrow to utilize the material in the normal control of maturation of the red blood cells

The disease is said to occur in persons from early adult life to old age both sexes are affected equally although in their latest publication Israels and Wilkinson state[101] that there is a tendency for it to occur more frequently in young women These authors describe the course as chronic with an insidious onset Ultimately the condition is fatal but life may be prolonged by blood transfusions and intensive liver extract therapy In treating such patients they recommend in terms of the U S P that 1 c c containing 15 units be given daily for 1 to 2 weeks to be followed by a similar dosage thereafter once or twice weekly

Although the reports of Wilkinson and Israels seem to be convincing some scepticism concerning the existence of such a disease has been expressed and the hematologists of this country are inclined to classify it under the heading of aplastic anemia The objection to this is that the bone marrow of patients with aplastic anemia is thought by some never to resemble pernicious anemia whereas in achrestic anemia it does so very closely It is possible however that they may be dealing with an aplastic anemia in which there is a hyperplasia of the bone marrow with a maturation arrest Such a condition would be classified as a pseudoaplastic anemia by some This condition however never shows a response to antipernicious anemia medication I have not encountered a case which fulfills the diagnostic criteria of achrestic anemia as given by Israels and Wilkinson

MACROCYTIC ANEMIA DUE TO *DIPHYLLOBOTHRIUM LATUM* (DIBOTHRIOCEPHALATUS ANEMIA)

The occurrence of this type of anemia in the United States is rare and most cases which are observed arise in Europe and their infesting parasites are brought by the individual to this country In recent years however, it has been determined that certain varieties of pike and perch in the large lakes in the north central part of the United States and the nearby provinces of Canada harbor the parasite and may transmit the infestation to natives of this country The chief interest in the condition lies in the fact that this parasite may be responsible for a macrocytic anemia, which is identical with that of Addisonian pernicious anemia in all respects, and one which is amenable to liver therapy or can be cured completely by expulsion of the worm

There are, however, some important differences between the anemia due to the tapeworm infestation and pernicious anemia, namely, (1) in tapeworm anemia free hydrochloric acid is present in about 16 per cent of the cases (2) in some instances, in which there is an achlorhydria, the acid may return when the worm is expelled, (3) the age group is somewhat different, for in the parasitic infestation there are two peaks to the curve of age incidence, one in the third and the other in the fifth or sixth decades (4) the disease can be cured in most instances by expelling the worm, (5) neural manifestations with the fully developed picture of subacute combined degeneration of the spinal cord in the parasitic anemia are rare, but they do occur

There has been a growing tendency in the United States to interpret the association of a macrocytic anemia with the presence of the intestinal parasite as a fortuitous situation, but this is certainly not correct in all instances It appears to be the most plausible explanation of the circumstances to conclude as follows (1) In some patients the association is nothing more than one of chance that is a person who becomes infested with the parasite happens to have pernicious anemia, (2) In other instances the parasite may cause an anemia which is identical with true pernicious anemia from a clinical and hematological standpoint as well as characteristic changes in the bone marrow, (3) A certain constitutional or hereditary influence in some unknown manner plays an important role in rendering some individuals susceptible to the action of the worm

The obvious treatment is to remove the parasite by the usual aspidium therapy The patient then should be kept under observation to note if following this there is a reticulocyte rise and an increase in the red blood cell count to normal If this does occur then it must be assumed that the anemia is due to the parasite, and no further treatment is indicated except to determine that there is no recurrence of the worm due to its incomplete removal If improvement does not follow expulsion of the parasite, then the anemia must be considered a

coincidental one and the proper antipernicious anemia medication therapy should be instituted

MACROCYTIC ANEMIA ASSOCIATED WITH HYPOTHYROIDISM

It is recognized that a macrocytic anemia may occur in patients with spontaneous myxedema following total thyroidectomy[109] and after removal of the thyroid gland[108] in experimental animals That a macrocytic anemia is the characteristic anemia of myxedema is a reasonable assumption because it is the type which is associated most commonly and it is curable solely by the administration of desiccated thyroid gland When such an anemia is present the red blood cell count usually is from 3 0 to 3 5 millions per cubic millimeter and the hemoglobin between 60 and 70 per cent The mean corpuscular volume usually varies from 100 to 110 cubic microns and the mean corpuscular hemoglobin concentration is characteristically within normal limits that is between 30 and 33 per cent It should be noted that anisocytosis never is pronounced and poikilocytosis is not observed as these are points which are of importance in differentiating the blood in this condition from pernicious anemia Although the reticulocytes may be slightly above 1 per cent rarely if ever is there striking evidence of active red blood cell regeneration

The blood picture as outlined above resembles in some respects that of a patient with pernicious anemia in a stage of mild relapse It should be kept in mind furthermore that in about one half of the patients with myxedema there may be an achlorhydria after the subcutaneous injecton of histamine A favorable response to liver or desiccated stomach is not observed in patients with myxedema but the blood will return slowly to normal following the use of desiccated thyroid gland The sternal marrow in patients with myxedema and an associated macrocytic anemia gives evidence of a hypoplastic state with a decrease in the number of nucleated red blood cells This picture is in striking contrast to the marrow of patients with pernicious anemia in which there is an increase in the nucleated cells of the marrow especially megaloblasts

The two conditions should not be confused as they resemble each other only superficially but it is not so rare to observe patients with fully developed myxedema receiving liver extract intramuscularly without benefit sometimes over long periods on the basis that they are thought to have pernicious anemia Although the appearance of the patient and the physical examination should differentiate the two conditions readily additional and conclusive diagnostic help may be secured from the determination of the basal metabolic rate which usually is − 20 to − 40 in myxedema and within normal limits or slightly elevated in pernicious anemia

Although a macrocytic anemia is the characteristic type in patients with

myxedema, 2 other varieties should be mentioned It is true that occasionally Addisonian pernicious anemia may be present also in a patient who has myxedema I have observed such a patient and others have been reported by Means Lerman and Castle[104] In my patient all of the clinical features of myxedema were present and in addition there was a red blood cell count of 480,000 per cubic millimeter and the blood findings fulfilled all of the criteria of true pernicious anemia Furthermore it was not possible to cure the anemia unless both desiccated thyroid and potent antipernicious anemia therapy were given simultaneously In any patient with myxedema and a macrocytic anemia with a red blood cell count which is below 3 0 million per cubic millimeter, the possibility of the two diseases being associated should be given consideration

There is a third type of anemia observed in patients with myxedema which should be mentioned This is a microcytic, hypochromic variety, which is observed especially in young adult women with hypothyroidism and in whom there is a profuse menstrual flow The anemia which is secondary to chronic blood loss is of the iron deficiency type and should respond to treatment with this metal If the hypothyroidism is not controlled however as it may be by desiccated thyroid therapy it is not always possible to bring the blood to normal by iron medication, as blood will be lost at a greater rate than it can be regenerated

Sprue

Definition and General Description

The sprue syndrome according to the definition of Rodriguez Molina[105], when fully developed, is a chronic deficiency state characterized by an insidious onset, chronicity of symptoms progressive development of gastrointestinal disturbances, mainly dyspepsia, soreness of the tongue and mouth meteorism and diarrhea The stools are usually liquid, foamy grayish, with an offensive odor and frequently voluminous and fatty Stomatitis, glossitis atrophic gastritis and rectosigmoiditis are important findings A macrocytic ' hyperchromic anemia with a megaloblastic anemia accompanies over 90 per cent of the cases fever is present in about 40 per cent No attempt will be made here to describe the syndrome fully except to discuss the hematology in detail and the relation of the disease to pernicious anemia

Sprue was considered to occur originally only in tropical countries, but in more recent years a similar condition non tropical sprue or idiopathic steatorrhea has been observed in subtropical or even temperate zones The condition resembles sprue in that the anemia is identical and the general symptoms insofar as the anemia is concerned are the same In sprue there is also a similar type of

glossitis as is seen in pernicious anemia and in the former condition it may be even more intense The anemia responds to liver therapy with an increase in the reticulocytes and the number of red blood cells in the same manner in sprue as in pernicious anemia

There are however some important differences between the two diseases as follows The chief complaints in sprue often are pronounced digestive disturbances and especially the passage of the characteristic stools the neurological manifestations of pernicious anemia usually are absent in sprue a greater degree of emaciation is present more commonly and free hydrochloric acid is found in the gastric secretions of many of the patients with the latter disease

Hematology of Sprue

It is now recognized that in 90 per cent of the patients with this disorder there is a macrocytic anemia which is indistinguishable from that observed in patients with true Addisonian pernicious anemia The red blood cell count may vary from a level below 1 0 million per cubic millimeter to approximately normal depending on the stage of the disease Likewise the hemoglobin conten of the circulating blood may vary from 4 0 to 16 grams (26 to 110 per cent) As in pernicious anemia the color index usually is high generally being in the vicinity of 1 0 The mean corpuscular volume is most frequently from 110 to 130 cubic microns and in some instances it may even be higher than this The mean corpuscular hemoglobin concentration commonly is in the vicinity of 32 to 33 per cent and the mean corpuscular hemoglobin about 40 micromicrograms From the findings given above it is clear that the changes in the circulating blood in sprue are similar in all respects to those in pernicious anemia

Examination of a stained blood film of patients with sprue shows varying degrees of macrocytosis anisocytosis and poikilocytosis These changes become more pronounced as the anemia increases in severity It is unusual however to see bizarre forms of erythrocytes which are so commonly present in pernicious anemia The leukocyte count characteristically is low usually being in the vicinity of 5 000 per cubic millimeter or less and the same type of multilobed neutrophils are present in the blood as are seen in pernicious anemia An eosinophilia is present but this is attributed by some to a helminth infestation which frequently is associated It is true that those patients without this complication usually do not have an increase in the eosinophils In sprue there is usually a reduction in the number of platelets when the anemia is severe and the reticulocytes average between 1 and 2 per cent in the untreated cases

When liver extract is given intramuscularly there is a striking increase in the number of reticulocytes in the circulating blood which is followed by a rise in the number of red blood cells in a manner entirely similar to the changes

observed in pernicious anemia, when antipernicious anemia medication is administered Moreover the patients with sprue experience the same dramatic sense of well being the improvement in the appetite the disappearance of the glossitis and the rapid gain in strength as seen in patients with pernicious anemia following effective therapy The gastrointestinal complaints disappear in most instances after the treatment with liver has been continued for several weeks

The remarkable therapeutic effects of synthetic folic acid, reported by Darby and Jones[105( )] and by Spies and his associates[47( )], strongly suggest that this form of therapy will be the one of choice in the future Additional studies are desirable however, to determine the exact dosages of the preparation and to observe the continued effect of the medication before an opinion can be offered concerning its definite value

Recently Suarez[105(b)] stated that the response of patients with sprue to folic acid, when given orally or intramuscularly, is as dramatic and satisfactory as that observed following the administration of liver extract When this material is given by mouth in doses of 10 to 20 milligrams daily, the patient experiences a sense of well being within three to four days, the number of reticulocytes increases in the peripheral blood, the condition of the tongue improves gaseous distension is less and anorexia disappears The total red blood cell count increases at about the same rate as in patients with pernicious anemia following liver extract therapy It is concluded by Suarez that, when the red blood cell count reaches normal probably 1 5 to 2 0 milligrams by mouth daily is all that is necessary to maintain it at that level Further conclusions by this observer were that, when a small dose is combined with an adequate diet, it is more effective and that small divided doses are more effective than when the same amount is given as a single large dose

One view in regard to the mechanism producing the anemia is presented by Shookhoff[106] According to this observer the macrocytic anemia of the disease may be divided into 3 types, depending on their reaction to treatment as follows (1) those responding to the oral administration of the extrinsic factor (2) those not responding to the oral administration of the extrinsic factor but yielding to oral liver extract, (3) those responding only to parenteral therapy He infers therefore that the macrocytic anemia of the disease may be due to (1) a deficiency of the extrinsic factor (2) a reduction in the intrinsic factor or (3) a failure of adequate absorption of the hematopoietic principle or a combination of two or more of these mechanisms

In a small percentage of the cases of sprue the anemia may be normocytic or hypochromic and microcytic It is probable that in such instances there is an associated iron deficiency which may be due to a diminished intake of the metal to impaired absorption of it or possibly to the chronic loss of blood from the lesions in the gastrointestinal tract

Idiopathic Steatorrhea and Celiac Disease

Relationship to Sprue

In 1888 Samuel Gee first described a condition occurring in England which he called celiac affection as a disease characterized by emaciation and the passage of pale bulky and offensive stools observed especially in children Later it was recognized that it might also be present in adolescents adults and even in old age The term idiopathic steatorrhea was applied to the disorder in adults to distinguish it from the steatorrhea which developed from a deficiency of bile or pancreatic juice Later it was determined that there were other manifestations of the condition in addition to emaciation and fatty stools namely infantalism tetany, rickets osteomalacia anemias of various types and mega colon

In more recent years it has been recognized that idiopathic steatorrhea is a term which now should be regarded as synonomous with non tropical sprue celiac disease and tropical sprue All of these conditions have much in common and hence probably should be considered as varieties of the same disease There does not seem to be any radical differences between non tropical sprue as observed in temperate climates and tropical sprue but whether these conditions represent different aspects of the same disease is still a matter of dispute[107, 108] Furthermore celiac disease as seen in England has many features of sprue and if it occurred in the tropics probably would be regarded as such although the latter condition does not commonly have its onset in childhood

Blood in Idiopathic Steatorrhea

In this disorder the blood may be (1) normal or show ( ) hypochromic anemia (3) a macrocytic anemia or (4) erythroblastic anemia The hypochromic anemia responds to iron and the macrocytic anemia to autolyzed yeast and liver extract In idiopathic steatorrhea the macrocytic anemia appears to be identical with that which occurs in sprue in tropical macrocytic anemia and in association with gastrocolic fistula but it differs in some respects from true Addisonian anemia In the non pernicious anemia group the blood bilirubin usually is within normal limits and poikilocytosis is absent In all of these conditions glossitis commonly is present but neural changes are observed rarely in sprue and allied conditions

Macrocytic Anemia in Pellagra

It is apparent from studies during the past few years that a macrocytic anemia may or may not be present in patients suffering from pellagra Spies and Chinn[109]

have reported that in 30 patients with the disease an anemia was present in almost two thirds and that in a majority it was macrocytic in type On the other hand Turner[110] states that in a group of 50 patients with the disease studied in the southern part of the United States there was an anemia present in only 16 per cent of the group, and in no instance was it macrocytic in type

In a study of 10 patients in Alabama who showed or had showed the clinical manifestations of pellagra, Moore and his associates[111] found severe degrees of macrocytic anemia present Bone marrow punctures indicated a shift to the younger red blood cell elements with a striking increase in megalocytes, a situation which resembled the changes in the bone marrow of patients with pernicious anemia during relapse These investigators concluded that the anemia resulted from a deficiency of both the extrinsic factor and poor absorption from the gastrointestinal tract This view is supported by the following evidence (1) it was demonstrated that the intrinsic factor was present in the gastric secretions of 3 of the patients, (2) in all instances there was a decided deficiency of animal protein in the diet, (3) 6 patients responded maximally to the administration of 250 grams of beef daily, (4) an alcoholic extract of beef muscle which is practically free from protein, produced a reticulocyte rise and a slight red blood cell increase (5) the crystalline members of the vitamin B complex were given orally, apparently without effect, (6) after the observations just described were carried out intramuscular injection of liver extract in 9 of the 10 patients produced a significant increase in the reticulocytes of the circulating blood and an acceleration of the red blood cell formation

It seems clear, therefore from the work of Moore and his associates that a macrocytic anemia is not rare in patients with pellagra, and that it is not due to a deficiency of the intrinsic factor, as it is in pernicious anemia, but that it results from a decrease in the extrinsic factor in the diet and from malabsorption from the intestinal tract The fact that synthetic folic acid (*L casei* factor) is effective in treating the macrocytic anemia of pellagra[46] is of interest but it does not in the light of our present knowledge explain the mechanism of the production of this type of anemia in pellagra There is a possibility also that extensive liver damage may be responsible in part for the anemia In one patient however studied by Sydenstricker and his associates[112], the antipernicious anemia factor was found to be present in the liver at necropsy

Macrocytic Anemia in Space Consuming Lesions of Bone Marrow

As indicated by the mean corpuscular volume it is not common to observe a pronounced marcocytic anemia myelophthisic anemia in space consuming lesions of the bone marrow In most instances in such anemias the mean corpuscular volume is within the accepted normal limits of 86 to 96 cubic microns as is the mean

corpuscular hemoglobin concentration The color index usually is in the vicinity of 1 0 The anemia therefore in such conditions is properly described in most instances as normocytic and normochromic It is true however that in some cases the mean corpuscular volume is slightly increased but ordinarily it is not more than 100 to 110 cubic microns and there is a normal amount of hemoglobin per cell present The erroneous impression is often gained however when a stained blood film from a patient with this condition is examined and measurements are not taken that a definite macrocytic anemia is present Such an anemia as emphasized by Mettier[118] may be observed in cases of myelosclerosis, osteosclerosis neurofibromatosis Gaucher s disease carcinomatosis and multiple myeloma It is also present in the leukemias and when such blood diseases are in the subleukemic stage the condition not infrequently is confused with pernicious anemia The blood picture in such disorders is that of a moderately severe anemia with leukopenia and the presence of myeloblasts and normoblasts in the circulating blood

In my experience the subleukemic stage of leukemia has been confused with that of pernicious anemia more frequently than any other type of severe anemia In patients with such a condition when there are no palpable lymph nodes or splenomegaly and if there is an achlorhydria and only a few or no immature cells in the circulating blood the differential diagnosis from pernicious anemia may be exceedingly difficult without the aid of a therapeutic trial of antipernicious anemia therapy and a sternal puncture

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ANEMIAS OF PREGNANCY

Classification and Definition

The anemias of pregnancy may be classified under the following headings

1 Physiological anemia
2 Microcytic hypochromic anemia, due to iron deficiency
3 Macrocytic anemia
4 Anemias incidentally associated with the gravid state

Definition — A true anemia of pregnancy may be defined as one due primarily to the gravid state in which the hemoglobin the red blood cell count or both are below the levels regarded as normal in pregnant women By this definition is excluded the physiological anemia of pregnancy which cannot be regarded as an abnormal condition In such an anemia the studies at the University of Michigan by Bethell[1] have shown that with the physiological anemia of pregnancy, which is due to blood dilution, the hemoglobin may be diminished to 10 grams per 100 c c of blood (64 per cent), and the red blood cell count to 3 5 millions per cubic millimeter Any true pathological anemia of pregnancy, therefore is one in which the hemoglobin or red blood cell count or both are lower than the levels given above as observed in the physiological anemia of pregnancy

History

It is stated usually that the earliest description of the anemia of pregnancy is that of Nasse[2] in 1836 but Osler[3] especially emphasizes the contributions of Channing in 1842 of Lembert in 1853 and Gusserow in 1871 The early report of Channing[4] well deserves a prominent place in the historical development of our knowledge of the anemias of pregnancy In his publication on anemia 9 of his cases were associated either with pregnancy or the puerperium It was his belief that the anemic state resulted from ' some less obvious and less appreciable cause' than bleeding Although there is no record that he performed a blood transfusion in any of these patients he recommended this as a desirable form of therapy

It was Spiegelberg[5] who in 1872 first called attention to the physiological anemia of pregnancy He demonstrated that there was an increased blood volume in pregnant dogs and postulated that the same process occurred in pregnant women In more recent years numerous attempts have been made to establish the occurrence and estimate the increase in the blood volume in pregnancy Among those who have contributed valuable information, which has a bearing

on this condition have been Miller Keith and Rowntree[6] and Schoenholtz[7] A review of the literature dealing with the physiological anemia of pregnancy has been published by Dieckmann and Wegner[8]

Osler s classical paper on The Severest Anemias of Pregnancy and the Post partum State which appeared in the British Medical Journal during 1919[9] did much to emphasize the importance of these anemias and it also contains an admirable summary of the literature to date In 1918 Schmidt[10] described four cases of pernicious anemia of pregnancy and deserves credit for emphasizing the importance of blood transfusions in the treatment of the condition The prediction that a macrocytic anemia of this type would be benefited by liver therapy was made by Murdock[11] and the earliest cases treated by this form of therapy were reported by Deschamps and Froyez[12] Audebert and Fabre[13] Brault[14] and Peterson, Field and Morgan[15] The initial case observed to have been benefited by desiccated defatted hog s stomach (ventriculin) was reported by Wilkinson[16]

Of special interest has been the development of our knowledge in recent years of the macrocytic anemia of native women in India In 1927 McSwiney[17] observed an incidence of 1 69 per cent of such an anemia in the native women of Calcutta In the same year Balfour[18] reported 150 cases seen in Bombay over a period of one and one half years Lucy Wills and her associates[19] [0] also directed attention to this type of anemia with excellent therapeutic studies It is recog nized however that in India this same type of anemia also occurs in non pregnant women and in men

The highly important work of Bethell[1] showing the relationship between the protein intake and the macrocytic anemia of pregnancy was first published in 1936

Physiological Anemia of Pregnancy

It has long been recognized that in all pregnant women there is normally a progressive decline in the number of red blood cells and the hemoglobin content of the circulating blood This begins early in pregnancy and reaches its maximum at about the sixth month after which it remains constant until about 2 weeks following parturition at which time the blood usually returns to normal These changes are known to be associated with an increase in the plasma volume of the circulating blood which decreases by dilution the concentration of both the red blood cells and the hemoglobin The erythrocytes however appear normal in size and shape There is apparently a compensatory increase in the leukocytes which accounts for their presence in normal numbers

In careful studies on normal pregnant women it was determined by Bethell and his associates[1] as previously stated that the lower limits of the normal

erythrocyte count during the course of pregnancy should be regarded as 3 5 millions per cubic millimeter and the hemoglobin as 10 grams per 100 c c of blood 64 per cent of the normal which is assumed to be 15 6 grams per 100 c c of blood Any determinations, which fall below these standards during the course of pregnancy, therefore, are indicative of a pathological anemia

It should be noted also that the increase of the plasma volume accentuates a preexisting anemia and, therefore makes more apparent the reduction in the red blood cells and hemoglobin This factor may have the effect of converting an exceedingly mild anemia into one of moderate severity during pregnancy

Incidence of Anemia of Pregnancy

Studies made several years ago [1] at the University of Michigan showed that the anemias of pregnancy are exceedingly common and furthermore that they are amenable to treatment with simple, effective and inexpensive remedies It was found by Bethell and Blecha[2] that 54 per cent of all supposedly healthy pregnant women, who came to our obstetrical out patient department, had a pathological anemia Additional observations made in two large rural counties of Michigan showed that in these areas a pathological anemia was present in 30 per cent of all cases examined in a large series of supposedly normal pregnant women If it is true that at any given time there are 2,500 000 pregnant women in the United States and if it can be assumed that 30 per cent of them have a pathological anemia of pregnancy, it would mean that 750,000 women are suffering at any given moment in this country from an easily controlled condition which if untreated, is a hazard to both the mother and the child If these figures could be applied to the world at large, especially in those regions in which there is frank undernutrition, the enormity of the problem is obvious

Of the two main pathological anemias of pregnancy, the macrocytic and the microcytic hypochromic type the latter which is associated with an iron deficiency is the most common In the 54 per cent of patients observed in the out patient department of the University of Michigan Hospital with an anemia it was found that 27 per cent had the iron deficiency type and 15 per cent the macrocytic variety In 12 per cent it was considered that both etiological factors were present

Iron Deficiency Anemia of Pregnancy

During pregnancy it is recognized that there is a notable increase in the iron requirements due (1) to the fetal demands (2) to the need for additional iron to form hemoglobin for the production of an increased number of erythrocytes in the maternal organism in an attempt to compensate for the anemia due to the

increased plasma volume (3) to meet the requirements due to the formation of increased maternal tissues Another factor which is of possible importance is the presence of an achlorhydria or hypochlorhydria which not infrequently is associated with the gravid state It is known that such a change impairs the normal absorption of iron from the gastrointestinal tract

Although iron is required in increased amounts during pregnancy, it is recognized that there is some conservation of the metal as the result of the absence of 10 menstrual periods Although there are diverse opinions concerning this question it appears to be a logical assumption that the following statement is a fair representation of the situation The requirements of normal pregnancy including an average amount of bleeding at delivery probably is two or three times greater than the loss by normal menstruation over a corresponding interval

It should be emphasized that if the pregnant woman cannot receive a sufficient quantity of iron from the diet to supply all of the increased needs incident to the gravid state, then she must depend on preexisting stores of the metal for the satisfaction of the fetal needs and the prevention of maternal anemia If this is inadequate for the maternal requirements an iron deficiency anemia will develop. Factors which play an important rôle in the creation of such stores prior to pregnancy and also in some instances during the pregnant state are an habitually low iron dietary intake gastrointestinal disorders hypermenorrhea and frequently repeated pregnancies It should be emphasized therefore that probably the most important factors in the etiology of the iron deficiency anemias of pregnancy are (1) the increased iron requirement during the pregnant state which makes necessary the utilization of the maternal reserve stores and ( ) a slight iron deficiency anemia which is present prior to pregnancy thus indicating that the iron reserves even before conception occurred were inadequate

Another factor which must be considered i the accentuation of a preexisting anemia which results from the normal increase in plasma volume This is known to occur during pregnancy with the maximum dilution at about the sixth month For example studies have shown that the greatest blood dilution at this time is about 26 per cent and therefore it can be calculated that, if the hemoglobin before pregnancy was 70 per cent this change alone at the sixth month would reduce it to approximately 58 per cent

Regardless of how such an anemia is produced there is no difference of opinion concerning the fact that it is attributable to a deficiency of iron This is established clearly by the fact that the administration of small doses of the metal will restore promptly the blood to normal and give assurance that the fetus will develop with adequate iron reserves

The relation of the iron intake in the food and the existence of a hypochromic anemia were made clear by the studies of Bethell and Blecha[22] In a survey of the blood of 34 patients during pregnancy it was found that when the daily intake

erythrocyte count during the course of pregnancy should be regarded as 3 5 millions per cubic millimeter and the hemoglobin as 10 grams per 100 c c of blood 64 per cent of the normal which is assumed to be 15 6 grams per 100 c.c of blood Any determinations, which fall below these standards during the course of pregnancy, therefore, are indicative of a pathological anemia

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cent exhibited an anemia of this type Of 159 out patients in the maternity clinic most of whom were of the indigent or low income groups, 27 per cent were found to have such a change in the blood During the course of studies carried out in the rural districts of Michigan in which the blood of 484 pregnant women was examined about 8 per cent of the subjects had a macrocytic anemia of clinical significance They were of a higher economic level than the groups previously mentioned and probably had a more satisfactory diet which accounts for the lower incidence of this variety of anemia

Etiology of Macrocytic Anemia of Pregnancy

For many years the etiology of this form of anemia was as obscure as that of true pernicious anemia By some it was considered to be a form of the latter disease others have thought more recently that it resulted from a transient depression of the intrinsic factor of the gastric juice which occurred during the pregnant state

In my opinion neither of these views concerning the etiology are correct The studies of Bethell and his associates[1] have established clearly to me the etiological factor responsible for such an anemia These investigators found that the incidence of the anemia is in inverse proportion to the amount of animal protein in the diet Their observations indicated that such an anemia was not present in pregnant women who partook of a diet containing animal protein to the amount of 50 grams or more With an intake of 30 to 49 grams daily it was present in 10 per cent of the patients and with one to 30 grams daily or less in 14 per cent It was found by Goldhamer and his collaborators[3] that the addition of protein to the diet of a person with an extreme macrocytic anemia of pregnancy caused the blood to return to normal without additional therapy

It has been shown by Bethell[10] that this type of anemia is amenable to the administration of a minimum amount of 85 grams of protein of which at least 50 grams is of the animal form From these observations it is clear that a protein deficiency is related to the macrocytic anemia of pregnancy Just how this exerts it effect however is a matter still under consideration There is of course the likelihood that the protein lack means a deficiency of the extrinsic factor which is readily supplied by the meat and eggs when added to the diet This could explain the prompt and beneficial effects of such therapy That either the extrinsic or intrinsic factor is diminished is suggested strongly by the fact that the intramuscular injection of liver extract acts as specific therapy in this form of anemia

No one has proven that there is a deficiency of the intrinsic factor in such patients If this is true it must be transient because the patients may recover and may never thereafter suffer from the condition The possibility has been sug

of iron was 16 milligrams or more hypochromic anemia was not present On the other hand when the intake was less than 8 milligrams daily, hypochromic anemia was present in 40 per cent of the women

Blood in Patients with Iron Deficiency Anemia of Pregnancy

The blood in this condition shows exactly the same changes observed in non pregnant patients with a hypochromic anemia Most frequently the red blood cell count is between 3 0 and 4 0 millions per cubic millimeter, the mean corpuscular volume usually is below 86 cubic microns and the hemoglobin from 8 00 to 10 00 grams per 100 c c of blood (51 to 64 per cent) In some instances the anemia may be due to two factors One an iron deficiency which causes a reduction in the amount of hemoglobin per cell The other, a deficiency of protein, which causes the number of cells to be reduced, but often they are normal or increased in size as shown by a normal or greater than normal mean corpuscular volume Such an anemia would be classified as a hypochromic, normocytic or macrocytic type In this variety of anemia the hemoglobin content of the blood would be less than 10 00 grams (64 per cent) and the red blood cell count below 3 5 millions per cubic millimeter

The use of iron in this variety of anemia of pregnancy is discussed under the general section of the treatment of the anemias of pregnancy

Macrocytic Anemia of Pregnancy

Macrocytic anemia has been known to be associated with the gravid state for many years and because of its resemblance to Addisonian pernicious anemia it has been called the pernicious anemia of pregnancy" Although the blood picture may be identical it differs from true pernicious anemia in several important respects It is seen more commonly in women below the age of 40 years free hydrochloric acid is present in the gastric secretions in about one half of the cases neurological complications are absent and recovery may follow transfusions or the termination of the pregnancy In more later years it has been found to respond favorably to the administration of liver extract and also to a high protein diet It differs also from pernicious anemia in that it does not always recur in subsequent pregnancies One should be careful to differentiate these cases from those in which a patient with true pernicious anemia becomes pregnant as has happened in several patients under my observation

The occurrence of a mild macrocytic anemia during the course of pregnancy is *not uncommon as shown by the figures of Bethell and Blecha*[22] *These* observers found that of 70 patients of distinctly low economic status admitted to the Maternity Unit of the University of Michigan Hospital, approximately 26 per

cent exhibited an anemia of this type Of 159 out patients in the maternity clinic most of whom were of the indigent or low income groups 27 per cent were found to have such a change in the blood During the course of studies carried out in the rural districts of Michigan in which the blood of 484 pregnant women was examined about 8 per cent of the subjects had a macrocytic anemia of clinical significance They were of a higher economic level than the groups previously mentioned and probably had a more satisfactory diet which accounts for the lower incidence of this variety of anemia

Etiology of Macrocytic Anemia of Pregnancy

For many years the etiology of this form of anemia was as obscure as that of true pernicious anemia By some it was considered to be a form of the latter disease, others have thought more recently that it resulted from a transient depression of the intrinsic factor of the gastric juice which occurred during the pregnant state

In my opinion neither of these views concerning the etiology are correct The studies of Bethell and his associates[1] have established clearly to me the etiological factor responsible for such an anemia These investigators found that the incidence of the anemia is in inverse proportion to the amount of animal protein in the diet Their observations indicated that such an anemia was not present in pregnant women who partook of a diet containing animal protein to the amount of 50 grams or more With an intake of 30 to 49 grams daily it was present in 10 per cent of the patients and with one to 30 grams daily or less in 14 per cent It was found by Goldhamer and his collaborators[13] that the addition of protein to the diet of a person with an extreme macrocytic anemia of pregnancy caused the blood to return to normal without additional therapy

It has been shown by Bethell[10] that this type of anemia is amenable to the administration of a minimum amount of 85 grams of protein of which at least 50 grams is of the animal form From these observations it is clear that a protein deficiency is related to the macrocytic anemia of pregnancy Just how this exerts its effect however is a matter still under consideration There is of course the likelihood that the protein lack means a deficiency of the extrinsic factor which is readily supplied by the meat and eggs when added to the diet This could explain the prompt and beneficial effects of such therapy That either the extrinsic or intrinsic factor is diminished is suggested strongly by the fact that the intramuscular injection of liver extract acts as specific therapy in this form of anemia

No one has proven that there is a deficiency of the intrinsic factor in such patients If this is true it must be transient because the patients may recover and may never thereafter suffer from the condition The possibility has been sug

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MACROCYTIC ANEMIA OF PREGNANCY

Macrocytic anemia has been known to be associated with the gravid state for many years and because of its resemblance to Addisonian pernicious anemia it has been called the "pernicious anemia of pregnancy." Although the blood picture may be identical it differs from true pernicious anemia in several important respects. It is seen more commonly in women below the age of 40 years, free hydrochloric acid is present in the gastric secretions in about one-half of the cases, neurological complications are absent and recovery may follow transfusions or the termination of the pregnancy. In more later years it has been found to respond favorably to the administration of liver extract and also to a high protein diet. It differs also from pernicious anemia in that it does not always recur in subsequent pregnancies. One should be careful to differentiate these cases from those in which a patient with true pernicious anemia becomes pregnant as has happened in several patients under my observation.

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Treatment of Anemias of Pregnancy

As these anemias are so prevalent, it would appear logical to employ effective preventive measures in their control in all pregnant women throughout the period of gestation This may be accomplished most effectively by simple measures which should be applied to all women as soon as the pregnancy is recognized The medication to be employed is of two types namely (1) ferrous sulfate in doses of 0 3 grams 3 times daily after meals in enteric coated capsules and (2) the assurance that the patient is receiving an adequate amount of protein in the diet The iron medication should be instituted routinely as soon as the state of pregnancy is known to exist even though no evidence of anemia is present It should be continued until several weeks after the termination of the pregnancy and throughout the period of lactation In respect to the diet attention should be directed to the protein intake especially protein of animal nature Every pregnant woman should have a minimum intake of 85 grams daily of which 50 at least should be of an animal nature This may be accomplished by giving the pregnant woman one quart of milk one fourth pound lean meat and two eggs daily By such simple means therefore it is possible to prevent both the hypochromic and macrocytic anemias of pregnancy in practically every case

The importance of these measures cannot be overestimated It often permits lactation which otherwise would not be possible convalescence is expedited puerperal infection is less likely and perhaps most important of all it makes certain that the infant will be born with adequate iron reserves If this were not done the hemoglobin and red blood cell count might be normal at birth but the infant is very likely to develop an iron deficiency anemia during the first year of life unless preventive measures are instituted

The treatment of the hypochromic anemia of pregnancy which has already developed does not differ from the prophylactic use of iron just discussed If the anemia is hypochromic then ferrous sulfate in the usual doses (0 3 gram three times a day after meals) should be prescribed Within 10 days to 2 weeks the amount should be doubled if there has not been a satisfactory response Some believe that it is better to administer the enteric coated pills in order to avoid gastric irritation but symptoms of the latter condition have never been trouble some in my experience Also I can state from a convincing experience that despite the favorable influence which the hydrochloric acid is known to exert on the utilization of iron in the body the enteric coating does not seem to impair the efficacy of the metal when given in this form

If there is a reduction in the red blood cell count below 3 5 millions per cubic millimeter then it is wise to be assured that the patient s diet contains at least 80 grams of protein daily of which 50 grams is of the animal variety as used in

gested[1] that a low protein diet may cause a fatty change in the liver and hence prevent this organ from performing its function of storage of the antipernicious anemia factor (the erythrocyte maturing factor) and thus become the cause of macrocytic anemia

While in most instances the anemia is mild, there is no question in my mind but what the so-called pernicious anemia of pregnancy, in which the red blood cell count and the hemoglobin of the circulating blood may be extremely low is merely an intensification of the milder variety of macrocytic anemia which is observed so commonly in the gravid state

In this connection the work of Watson and Castle[1] is of interest Recently they have emphasized the observations of previous investigators which has shown that there is a difference in the manner of response of macrocytic anemias which usually is associated with pregnancy in the tropics, from that shown by patients with the macrocytic anemia of Addisonian anemia In such macrocytic anemias of the tropics there is no response following the parenteral administration of liver extract of known potency but rapid blood regeneration occurs when liver extract liver or autolyzed yeast is given orally

These observations were confirmed by Watson and Castle in 3 females who have a macrocytic anemia apparently of this unusual type They conclude that (1) this demonstrates in these patients a deficiency of some substance other than the principle defective in pernicious anemia, (2) that possibly in this type of patient a new hemopoietic substance is formed from the liver extract in a fashion analogous to the food gastric factor relationship in Addisonian pernicious anemia and finally (3) that this distinction emphasizes the desirability of a therapeutic trial of orally administered liver extract in macrocytic anemias particularly those of pregnancy when they prove to be refractory to parenterally administered liver extracts

Blood Changes in Macrocytic Anemia of Pregnancy

In most instances the red blood cell count is in the vicinity of 3 0 to 3 5 millions per cubic millimeter and the hemoglobin from 9 3 to 10 9 grams per 100 c c of blood (60 to 70 per cent) The color index is 1 0 or higher and the mean corpuscular hemoglobin concentration 30 to 35 per cent There is usually a slight degree of macrocytosis as indicated by a mean corpuscular volume of from 100 to 110 cubic microns

In the most severe cases the red blood cell count may be as low as 1 0 million per cubic millimeter the hemoglobin from 20 to 30 per cent , and pronounced anisocytosis and poikilocytosis may be present The white blood cells are normal or reduced in numbers Such a blood picture is identical with that of pernicious anemia in a patient with severe relapse

Treatment of Anemias of Pregnancy

As these anemias are so prevalent it would appear logical to employ effective preventive measures in their control in all pregnant women throughout the period of gestation. This may be accomplished most effectively by simple measures which should be applied to all women as soon as the pregnancy is recognized. The medication to be employed is of two types, namely (1) ferrous sulfate in doses of 0.3 grams 3 times daily after meals in enteric coated capsules and (2) the assurance that the patient is receiving an adequate amount of protein in the diet. The iron medication should be instituted routinely as soon as the state of pregnancy is known to exist, even though no evidence of anemia is present. It should be continued until several weeks after the termination of the pregnancy and throughout the period of lactation. In respect to the diet attention should be directed to the protein intake, especially protein of animal nature. Every pregnant woman should have a minimum intake of 85 grams daily of which 50 at least should be of an animal nature. This may be accomplished by giving the pregnant woman one quart of milk, one fourth pound lean meat and two eggs daily. By such simple means, therefore, it is possible to prevent both the hypochromic and macrocytic anemias of pregnancy in practically every case.

The importance of these measures cannot be overestimated. It often permits lactation which otherwise would not be possible, convalescence is expedited, puerperal infection is less likely, and perhaps most important of all, it makes certain that the infant will be born with adequate iron reserves. If this were not done, the hemoglobin and red blood cell count might be normal at birth, but the infant is very likely to develop an iron deficiency anemia during the first year of life unless preventive measures are instituted.

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If there is a reduction in the red blood cell count below 3.5 millions per cubic millimeter, then it is wise to be assured that the patient's diet contains at least 80 grams of protein daily of which 50 grams is of the animal variety, as used in

the prophylactic treatment If the anemia is severe, both the iron medication and protein intake should be increased 50 per cent

In the presence of the rarely observed severe macrocytic anemia or the "pernicious anemia of pregnancy", in which the hemoglobin may be reduced to 30 or 40 per cent and the red blood cell count from 1 0 to 1 5 millions per cubic millimeter, then it may be wise to transfuse the patient several times At the same time oral iron medication should be begun in doses of ferrous sulfate 3 times daily after meals and most important of all, 1 c c of liver extract, containing 15 units should be administered intramuscularly daily for 1 week Thereafter 1 c c should be given 3 times weekly until the blood reaches normal

The iron medication is advised because with liver extract injections the red blood cell count usually increases more rapidly than does the hemoglobin percentage and consequently the color index and the mean corpuscular hemoglobin concentration may fall below normal There is no longer any indication to terminate the pregnancy as a therapeutic measure, a procedure which in previous years has been recommended by some

From the recent observations of Watson and Castle[4] and others it should be kept in mind that a therapeutic response may follow oral administration of liver extract when the parenterally administered preparation fails Certainly this form of oral therapy and also autolyzed yeast should be tried when the parenteral form of treatment is ineffective

COEXISTENCE OF VARIOUS BLOOD DISEASES WITH PREGNANCY

It is of course possible for patients with almost any type of blood disease to become pregnant, and the situation is then one in which two wholly unrelated conditions are present in the same person that is there is pregnancy with or without the anemia of this state and the fortuitously associated blood dyscrasia In my experience I have observed pregnant women with leukemia, pernicious anemia sickle cell anemia iron deficiency anemia and congenital hemolytic icterus

Of special interest is the coexistence of pregnancy and pernicious anemia Previously it has been thought that when a woman with pernicious anemia became pregnant it was an indication for a therapeutic abortion It has been my gratifying experience to observe several patients with the disease who have gone through pregnancy successfully and gave birth to a healthy normal infant Such patients should have the blood maintained at the normal level for pregnancy (hemoglobin of 10 0 grams and red blood cell count of 3 5 millions per cubic millimeter) by the administration of liver extract and the addition of at least one quart of milk two eggs and one fourth pound of lean meat daily Certainly there is no indication to terminate a pregnancy in such a patient This is because

with the treatment outlined there is every prospect that the maternal blood can be maintained at a normal level throughout the pregnancy and that the child will be healthy when born as far as this type of blood dyscrasia is concerned

Likewise it is possible for patients to go through pregnancy successfully while afflicted with chronic leukemia and give birth to a healthy child as this has happened in a woman under my observation In such cases however it becomes necessary to withhold roentgen ray treatment because of the possibility of producing monster like changes in the child It does no harm however to give the mother repeated blood transfusions but probably it is wise to defer treatment with arsenic also in the interests of the fetus

Recently Hurwitt and Field[5] have reported the case of a 27 year-old woman whose death resulted in the fourteenth week of pregnancy from idiopathic aplastic anemia After reviewing the literature they conclude that the association of this variety of anemia with pregnancy is more than coincidental In other words they believe that the gravidity may play an etiological or conditioning rôle It is their opinion that in the presence of such an anemia interruption of the pregnancy should be considered strongly

In general it is my opinion that with the modern development of the treatment of the anemias including the effective use of liver iron and blood transfusions therapeutic abortion is rarely if ever, indicated in women with any type of blood dyscrasia

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HEMOLYTIC ANEMIAS

CLASSIFICATION

There is no classification of these anemias which is entirely acceptable to all of those who have made a study of the subject This is chiefly because there are divers opinions concerning the fundamental causes of the increased destruction of erythrocytes in this type of anemia Considerable clarification of the subject would result if the normal mode of blood destruction were known

The following classification which appears in Clinical Laboratory Diagnosis and Essentials of Hematology' as prepared primarily for the students at the University of Michigan Medical School by Dr Frank H Bethell is as brief and as satisfactory as any yet presented

I ACUTE HEMOLYTIC ANEMIA

1 Sepsis bacterial toxins *B welchii*, streptococcus etc

2 Protozoa malaria Oroya fever (Bartonella)

3 Poisons benzene compounds lead etc

4 Drugs sulfonamide compounds acetanelid nitrites

5 Allergic sensitization hemolysins paroxysmal hemoglobinuria favism

6 Transfusions of incompatible blood agglutinins and hemolysins

7 Lederer s anemia an acute febrile anemia of childhood which may be precipitated by infections and appears to be due to hemolysins

8 Marchi Micheli syndrome paroxysmal nocturnal hemoglobinuria

9 March hemoglobinuria

10 Toxic products of metabolism as in some cases of leukemia and Hodgkin s disease

II CHRONIC HEMOLYTIC ANEMIA

1 Acquired (a) Most of the conditions listed under the acute anemias when acting less intensively and for a more prolonged period may be responsible for a chronic hemolytic anemia

(b) Chronic acquired hemolytic anemia of obscure origin probably associated with the presence of iso-hemolysins

2 Congenital

(a) Congenital hemolytic jaundice (familial acholuric icterus)

(b) Sickle cell anemia

(c) Oval cell anemia

(d) Erythroblastic anemia

(e) Cooley s anemia

History

Usually it is stated that Murchison in 1877[1] was the first to recognize chronic hemolytic anemia and it is true that he did describe cases with persistent and hereditary jaundice The greatest credit however should be accorded Vanlair and Masius who in 1871 first described the hereditary nature of the jaundice and the typical microspherocytes of the disease 6 years before the publication of Murchison

The initial accurate and complete details of the clinical picture of chronic hemolytic jaundice were given by Oscar Minkowski[3] one of Naunyn s distinguished pupils before the Deutsch Gesellschaft fur Innere Medicin at its eighteenth meeting held in Wiesbaden in April 1900 He described the condition as an hereditary affection characterized by chronic jaundice urobilinuria splenomegaly and deposits of iron in the kidneys In a second more comprehensive paper published in 1905 Minkowski[4] reported the cases of 2 brothers who had been icteric since childhood with enlargement of the spleen and urobilinuria

Two of the special and highly significant characteristics of the blood in this condition were discovered by Chauffard namely, the increase in the fragility of the red blood cells to hypotonic salt solutions[5] and the fact that the reticulocytes were increased in number[6] Eppinger and Charnas in 1913[7] were the first to call attention to the striking increase in fecal urobilinogen in cases of hemolytic jaundice The observation that the blood bilirubin was elevated was made by van den Bergh in 1916[8]

Splenectomy was performed first in 1907 on a patient with hemolytic jaundice acquired but with a fatal result in a patient by Vaquez and Giroux[9] The operation was accomplished successfully in a second patient however, by Micheli in 1911[10]

The first general article dealing with this operation was written by Eppinger and Ranzi in 1914[11]

The acquired type of hemolytic jaundice was discussed originally by Widal Abrami and Brule in 1907[12], although apparently Hayem[13] had recognized similar cases in 1898 This type of anemia was investigated by the French school of hematologists and studies on fragility, reticulocytoses, auto-agglutination and hemolysins were made by Chauffard and his associates, especially between the years 1907 and 1909 and by Widal and his pupils during the same interval of time

In 1925 the report of Lederer[14] dealing with acute hemolytic anemia was regarded as the description of a new clinical entity, but as Dameshek and Schwartz[15] say this was a rediscovery of a syndrome which had been lost sight of for more than a decade

Main Views Concerning the Mechanism of Abnormal Hemolysis in Hemolytic Anemias

It should be recognized that our knowledge concerning this subject is incomplete and hence much of the material offered in explanation of the hemolytic states is purely speculative and must be accepted on a tentative basis If the normal mechanism of blood destruction were known it might be possible to say that this process is due to multiple causes and that also in any one of the specific types of hemolytic anemias several different mechanisms may be active

The various theories which at present are receiving chief attention are as follows

(1) A hereditary defect in the red blood cells It is held by the proponents[16] of this theory that the increased hemolysis may result from the inheritance of cells which are more spherical and hence more easily destroyed than the normal biconcave erythrocytes

(2) The theory is proposed by Ham and Castle[17] that increased hemolysis may result from spheriodicity of the erythrocytes which may be associated with extreme stasis especially in the spleen

(3) It is contended especially by Dameshek and Schwartz[15] that the presence of hemolysins may be the underlying cause of many of the acute and chronic hemolytic anemias They believe that the spherocytosis and increased fragility of the red blood cells are merely indicative but not primarily causative of a hemolytic process

(4) Lysolecithin The theory of Bergenhem and Fahraeus[18] is that the normal blood contains a lytic substance to which the name lysolecithin has been given These investigators suggest that it becomes increased in amount with stasis and hence may be responsible for normal blood destruction in the spleen which is the chief organ of stasis in the body

(5) The spleen as a cause of hemolytic anemia The exact role of the spleen in the etiology of the hemolytic anemias still is unknown Some consider that as splenectomy in congenital hemolytic anemia and also in some cases of the acquired disorder results in a complete cure it must be the main cause of the anemia in such conditions

Others contend that the spleen is the chief organ of stasis in the body as previously emphasized and hence is important from the standpoint of hemolysis[17] another point of view is that splenomegaly is more the result than the cause of the hemolysis[19] some believe that the action of this organ and lysolecithin are closely related[18] Doan and his associates[9] hold that the spleen plays a rôle in the production of the hemolytic anemias simply because it represents the largest part of the reticuloendothelial system

Normal and Pathological Physiology of Hemolytic Syndromes

It is recognized that with the increased rate of destruction of hemoglobin the circulating bilirubin increases, and consequently a patient with hemolytic anemia develops a slight icteric tint. That there is a change in the blood bilirubin is indicated by the van den Bergh reaction which increases from a normal of 0.8 milligrams per 100 c.c. of blood to 1.5 milligrams or greater. The icterus index also increases from a normal of not greater than 5 units to 15 or 20 units.

By means of the "hemolytic index", as devised by Miller, Singer and Dameshek,[1] it is possible to determine the amount of urobilinogen which is excreted daily in the stools, and employ this as a measure of the rate of red blood cell destruction in the body. Normally this is between 11.1 and 20.8 milligrams of urobilinogen daily. Their studies have shown that a decreased index was present in patients with polycythemia, hypochromic anemia and in the post splenectomy state. In these conditions the decrease varied between 20 and 69 per cent. An increase was found in a number of conditions, as follows: pernicious anemia from 204 to 1,131 per cent; in congenital and acquired hemolytic anemia from 287 to 1,672 per cent; in Cooley's anemia from 700 to 2,159 per cent; and in one case of Gaucher's disease the increase was 61 per cent. While this reaction, the technic of which is given in the original article, is not feasible to apply in the routine study of patients in the clinic, it nevertheless gives important information from a theoretical standpoint, for it indicates clearly those disorders in which hemolysis plays an important role in the mechanism of the production of the anemia.

Changes Which Result from Hemolysis

It is considered that when hemolysis is present certain changes invariably develop which are directly or indirectly the result of this process. These are splenomegaly, hyperbilirubinemia, hyperplasia of the bone marrow with an increase in the nucleated erythrocytes as compared to the white blood cells and reticulocytosis which is taken as an indication of the increased activity of the erythroblastic tissue.

The nature of the changes associated with hemolysis depend to some extent on the rate of destruction of the red blood cells. For example, if there is extremely rapid destruction, hemoglobin will appear in the plasma and urine, conditions which are designated as hemoglobinemia and hemoglobinuria respectively. Hemosiderin, the iron containing derivative of hemoglobin, may be also present in the urine in severe cases of hemolytic anemia. Urinary casts composed largely of hemoglobin may be found likewise under these circumstances.

CONGENITAL HEMOLYTIC JAUNDICE

Synonyms — Chronic acholuric jaundice, chronic familial jaundice hemolytic splenomegaly spherocytic anemia spherocytic jaundice spherodocytic jaundice

Definition — A chronic hemolytic anemia with acute exacerbations characterized by a non obstructive jaundice without bilirubinuria with spherocytosis increased fragility of the red blood cells reticulocytosis and an enlarged spleen The condition is congenital and is transmitted as a mendelian dominant characteristic

Etiology

Age

The condition has been recognized in some infants even at the age of a few weeks or a few months The manifestations may be so mild that the disease is not detected until middle or late adult life

Sex and Race

Males and females are affected with equal frequency Previously it has been thought that the condition occurred in all races and climates although some discussion has arisen as to its frequency in the negro race Recently a report by Scherer and Cecil[22] has indicated that it is rare in this race but cases undoubtedly do occur

Heredity

It has been established definitely that the condition is an hereditary one and that it is transmitted as a mendelian dominant trait by either parent The mere statement that another case does not exist in the family is insufficient evidence to eliminate the condition and in all such instances an attempt should be made to examine the blood of both parents and other close consanguineous relatives

Pathogenesis

The details concerning the various theories in regard to the cause have been given in the introductory section dealing with the hemolytic anemias and hence will not be repeated here It suffices to say that the fundamental inherited cause of the disease that is the factor which is responsible for the increased destruction of the erythrocytes is not known, and there is by no means a unanimous opinion

regarding its possible nature The best summary in my opinion of our present conception of the pathogenesis of the disease is given by Lloyd[3] as follows ' The pathological blood destruction found in acholuric family jaundice is dependent upon the inheritance of an abnormality of the erythron As a result of this defect the red blood cells are abnormally susceptible to damage in their passage through the spleen but the process very probably causes little or no permanent damage to the normal erythrocyte It is not possible in the present state of knowledge of the physiology of the spleen to assert the nature of this destructive process but it seems probable that it is connected with the storage of red cells in the venous sinuses and with the formation of lysolecithin It is possible that lysolecithin is formed in the course of normal splenic function in such concentration as will cause permanent damage to the red cells of patients with acholuric family jaundice indicated by the spherocytosis which persists until the death of the cell but which is not sufficient to cause permanent alteration in the normal erythrocytes, a part of whose function may be the resynthesis *of lecithin*

Pathology

The spleen usually weighs between 1 000 and 1,500 grams but it has been observed to be as heavy as 3 500 grams Microscopically the outstanding feature is the enormous engorgement of the pulp with erythrocytes while the sinuses are relatively free from blood The changes in the spleen are interpreted by some[4] as indicating a condition of hyperactivity which suggests the morbid accentuation of an otherwise normal process The bone marrow is hyperplastic with the predominating cell the normoblast The fat in the long bones such as the femur and the humerus is replaced completely with red marrow There is also an increase in the number of myelocytes and megakarocytes The liver may be slightly increased in size but usually it is normal A common and important finding is the presence of bilirubin stones in the gall bladder in about 70 per cent of the patients Usually they are single but occasionally multiple and rarely numerous There are occasionally ulcers of the lower part of the leg in the region of the malleoli Usually they are persistent and refractory to all forms of treatment except splenectomy, following which they disappear promptly

Symptoms and Signs

The clinical manifestations of congenital hemolytic jaundice may be exceedingly variable but they can be classified conveniently under the following headings, (1) latent (2) chronic and (3) acute

In the latent variety there are no complaints and the only evidence of the

disorder is the presence of spherical red blood cells in the circulating blood or the tendency of some cells to be thicker than normal and somewhat increased in mean diameter Furthermore in such patients there is always presumably another case in the family but such a patient may be asymptomatic also It can be said however that there is no other case among the near blood relatives only after their blood has been examined The latent cases may become active at any time during the life of the individual from infancy to the fifth or sixth decades Once the disease has become active jaundice with splenomegaly is likely to persist throughout life unless a splenectomy is done

The chronic phase is characterized by a slight jaundice and a mild to moderate anemia To many of these patients may be applied the characterization which originated many years ago that they were more jaundiced rather than sick Their usual complaints are mainly referable to the fact that the jaundice is noticeable and that the symptoms of anemia such as weakness and ease of fatigue are present to a variable degree

The acute phases of the disease or crises which have been termed crise de deglobulinization by the French is characterized by a sudden increase in the severity of the anemia with an intensification of the jaundice abdominal pain fever and mild to severe degrees of shock

The jaundice which is the usual presenting symptom fluctuates widely in intensity but is rarely more than moderate in extent It may be apparent at birth or appear in childhood but occasionally it is not present until adult life Its intensity is not dependent solely on the degree of anemia but is related to three factors namely (1) the degree of fragility of the erythrocytes (2) the activity of the spleen (3) the extent of red blood cell destruction In crises particularly there is close parallelism between the anemia and the jaundice In the chronic phases of the disease as Watson points out[5] the ability of the liver to excrete bilirubin must be regarded as the most important factor if not the sole one in determining the degree of the jaundice

It is probable that the spleen is enlarged in every patient with this disease The absence of such a finding therefore should arouse legitimate doubt as to the correctness of the diagnosis of congenital hemolytic anemia In those rare cases in which it is not palpable during life it is nevertheless enlarged but not to the extent where it can be felt below the costal margin The usual degree of the enlargement is such that the non tender edge extends 5 to 6 centimeters below the costal margin It is said to be increased in size in some patients so that the edge extends to the umbilicus or the crest of the ilium In general it may be said that the more severe the anemia and the jaundice the larger the spleen but occasionally cases are encountered where the reverse of this is true

It has long been known that cholelithiasis is a common complication of chronic hemolytic jaundice This condition is due primarily to the excessive

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the hemoglobin from 60 to 80 per cent In some cases however, the changes may be much more extensive I have seen for example patients in the chronic phase of the disease with a red blood cell count in the vicinity of 2.0 millions per cubic millimeter and a hemoglobin of 30 to 40 per cent In a hemolytic crisis there is often an amazing acceleration in the destruction of the erythrocytes with an extremely rapid fall in the erythrocyte count to 1.0 million or even less and in the hemoglobin to 20 per cent or lower

There are three changes in the blood of patients which are peculiar to the disease and hence should be mentioned in some detail They are (1) the spherical shape of the cells (2) the increased fragility to hypotonic salt solutions (3) the reticulocytosis

Spherocytosis is shown in the blood of these patients by the presence in a stained blood film of small round deeply colored red corpuscles which are called spherocytes These cells form only a small or moderate number of the erythrocytes of the blood and many of the other red blood cells are larger especially the reticulocytes The spherocytes are always smaller that is they have a diameter below normal and also they are always thicker with a tendency toward a spherical shape The mean corpuscular volume which of course is the average volume of all the cells in the blood may be smaller larger or normal in size Observations have shown however, that the mean corpuscular volume most frequently is normal or slightly below normal in size usually fluctuating between 77 and 87 cubic microns In some instances these measurements may be increased to 100 to 120 microns or even higher It is known that the reticulocytes usually have a greater volume than the normal erythrocyte and this is another factor, which may influence the final determination as to whether the cells have an increased a normal or a decreased mean corpuscular volume

The *mean corpuscular hemoglobin* usually varies directly with the change of volume and the mean corpuscular hemoglobin concentration is ordinarily within normal limits of about 33 per cent but it may in some instances be elevated to as high as 37 to 39 per cent

From a diagnostic standpoint the *fragility test* is of great importance because the cell in the typical cases of congenital hemolytic icterus are always more fragile than normal In the average patient with the disease hemolysis resulting from hypotonic salt solutions usually begins at about 0.69 per cent and is complete at 0.39 whereas in the control the beginning hemolysis characteristically occurs at about 0.45 per cent and it is complete at 0.33 per cent It should be emphasized that the test rarely is positive in any condition except congenital hemolytic jaundice or the acquired type Extreme care should be taken in the technic of this test and a blood known to be normal always should be observed along with each determination of a patient s blood otherwise erroneous results may be reported

production of bilirubin as a result of the increased destruction of erythrocytes which favors the formation of bilirubin stones They are present in about 70 per cent of all patients with the disease The gall stones usually are single, almost always dark in color and have a rough nodular surface As they contain more than 50 per cent bilirubin they should be considered as pigment stones They contain a sufficient amount of opaque material to cast a shadow in the roentgen ray In occasional instances patients have been operated upon for gall stones and the underlying cause of the condition, the chronic hemolytic icterus has been overlooked

No changes occur in the long bones of these patients but in recent years it has been noted that alterations in the skull resembling those seen in Cooley's anemia and in sickle cell anemia, may be present These bone lesions are characterized by a peculiar thickening and formation of striations of the calvarium which give rise to the curious appearance aptly described as 'hair on end' In other patients the tower skull, turmschadel', and oxycephaly have been described It is probable that the skeletal deformity in any given case is proportional to the degree of hemolysis and the extent of the compensatory reaction of the bone marrow The bone changes in patients whom I have observed have been slight and rarely encountered

European observers [6, 27] have reported changes in the physical make up but these alterations which they consider to be distinctive although looked for have not been apparent in the patients I have seen Among those findings which have been mentioned are the tower skull protruding eyes abnormally wide base of the nose elevated palate prognathism and protruding teeth Severe symptoms in childhood may impair the normal rate of growth but this does not occur in the average patient with the disease

It is of interest to note that leg ulcers usually in the region of the malleoli may develop occasionally and remain refractory to all treatment except splenectomy The same condition occurs although more commonly, in patients with sickle cell anemia

Laboratory Findings

The Blood

The level of the *red blood cell count* and the *hemoglobin* depends on the stage in which the patient is observed In the latent phase the blood is normal or approximately so and no other abnormalities are found except some degree of spherocytosis, an increase in the number of reticulocytes and evidences of some decreased resistance to hypotonic salt solutions In the chronic stage the red blood cell count varies usually from 3 0 to 4 0 millions per cubic millimeter and

causes at any age but have a tendency to become less frequent as a patient passes through young adult life Such episodes are characterized by a sudden increase in the destruction of the erythrocytes marked by a deepening of the jaundice and an increase in the anemia and pallor With these changes there is weakness fever nausea vomiting abdominal pain and variable degrees of shock The size of the spleen and the degree of jaundice may vary within an hour

Recently Dameshek[23], who has observed 3 cases of acute hemolytic crises which developed in 2 brothers and a cousin in the same household within 10 days has proposed that such an acute state may be related to the action of a hemolysin similar in effect to a toxic chemical or immunological substance rather than an intrinsic defect in the red blood cells On the other hand per contra it has been suggested that the condition may be explained on the basis of some sudden increase in the activity of the spleen

Differential Diagnosis

The three essential diagnostic features of the malady are (1) the demonstration of the increased thickness or spherocytosis of the erythrocytes (2) the increased fragility of the red blood cells to hypotonic salt solutions (3) the presence of a reticulocyte count above normal in the peripheral blood In addition other important findings from a diagnostic standpoint are the acholuric jaundice the palpable spleen the presence of other cases in the consanguineous relatives and the history of a disease of long duration with intervals of remissions and exacerbations

The conditions with which congenital hemolytic jaundice are confused most frequently are pernicious anemia splenic anemia erythroblastic anemia and toxic hepatitis with anemia The differentiation from these diseases should not be difficult provided the proper hematological methods of study are employed It is the separation of the group of subacute or chronic acquired or atypical anemias with acholuric jaundice reticulocytosis and splenomegaly which causes the chief difficulty in the differential diagnosis of the condition A discussion of this will be given under the heading of *Chronic Acquired Hemolytic Jaundice*

Treatment

It is well established, in my opinion that splenectomy is the only form of successful treatment of congenital hemolytic jaundice Hence this operation should be performed in every patient as soon as feasible after the diagnosis has been established The results are highly satisfactory in almost all cases Failures have occurred in patients who probably had the acquired type of hemolytic jaundice

An increase in the *reticulocytes* of the circulating blood to 10 per cent or higher is one of the most constant findings in the blood of patients with this disorder and when absent this at once should arouse suspicion as to the diagnosis The increase in these cells must be interpreted as evidence of a compensatory effort on the part of the bone marrow to replace the erythrocytes lost from the circulating blood as a result of increased blood destruction In some instances the number of reticulocytes may be exceedingly high, as it was in one of my patients in whom 90 per cent of all red blood cells present in the circulating blood were of this type Although the reticulocyte count may be increased in many different types of anemia especially immediately following treatment with liver and with iron in no other condition is the count so persistently elevated to such a level as in congenital hemolytic anemia or in some instances of the acquired type In addition to the increased number of reticulocytes there is other evidence of activity of the bone marrow as shown by a certain amount of *polychromatophilia* and the presence of cells containing *Cabot's rings* and *Howell Jolly bodies* *Normoblasts* usually are in the circulating blood and in some cases they may be observed in large numbers

During the chronic phases of the disease the *leukocytes* most commonly are normal or slightly increased but in crises there may be a hyperleukocytosis with counts as high as 50 000 per cubic millimeter In such instances there may be a shift to the left ' of the neutrophils and as many as 10 per cent may be myelocytes Generally the blood platelet count is normal, but in some instances there may be unimportant changes above or below normal

Other Laboratory Tests

The icterus index always is elevated during the active phases of the disease, and usually it is found in the vicinity of 10 to 40 units the higher levels being in the hemolytic crises or when there is a complicating cholecystitis with or without stone The van den Bergh reaction is indirect or delayed with readings which vary from 1 0 to ? 5 milligrams per 100 c c

The urine is reddish yellow in color due to the excess of urobilin which is present almost constantly There is no bilirubin present in the urine in the uncomplicated cases and consequently the tests for bile are negative *Bile acids* and bile salts are not present in the urine or the blood plasma The feces have a pronounced deep yellowish brown color and contain from 20 to 30 times the normal amount of urobilin

HEMOLYTIC CRISES

These episodes which are regarded as acute exacerbations and are characterized by an intensification of all the symptoms of the disease occur from obscure

Treatment of Hemolytic Crises

This acute phase of the disease is one of serious moment and may lead to death unless measures are taken to treat the patient promptly In general it may be said that the recommended forms of therapy are employed in the hope that the resultant improvement will permit splenectomy as an emergency operation The most important therapeutic indication therefore is to replace the fluid electrolytes and red blood cells by means of blood transfusions It is recommended that a series of to 4 transfusions of 500 c c be given by the slow drip method with intervals of 4 to 6 hours between the transfusions To a child the same number of transfusions may be administered in amounts of 250 to 300 c c to each transfusion In the severe cases splenectomy should follow the transfusions after a period of 12 to 48 hours depending on the condition of the patient With the rapid destruction of blood during crises there is a sharp decrease in the blood volume, and the state of shock may be serious to combat In such patients if blood transfusions are not well tolerated as discussed in the following paragraph then plasma transfusions should be given

Repeated hemolytic crises should not be permitted to continue because they may be responsible for long periods of invalidism or the condition may terminate fatally The wisest procedure is to remove the spleen in a chronic period of the disease when the patient is in good shape for the operation and thereby avoid the possibility of operating during an acute crisis when there is greatly added hazard

Unfavorable Reactions to Whole Blood Transfusions

Even though all care is employed in matching the blood of the recipient and the donor, it has been known for some years that blood transfusions in patients with this disease may be followed by alarming symptoms and even a fatal termination The ominous effects of such transfusions have been emphasized by Doan and his associates[37( )] and others[37(b)] It is the belief of the former that the disturbing symptoms occur in patients with the most severe anemia Nevertheless it is recognized that some of the patients with an extremely low red blood cell count can tolerate blood transfusions without serious difficulty It is recommended however that when such a blood transfusion is given the following procedures should be carried out (1) that the blood be administered by the slow drip method (2) that 500 c c of blood be given with equal parts of 5 per cent dextrose solution over a period of about 3 hours (3) as the cause of death may be uremia associated with the deposition of hemoglobin in the tubules of the kidney it has been found that in animals[33] this may be averted by rendering the urine alkaline This may be accomplished readily in humans by giving an

in which improvement does not always follow the operation or because an accessory spleen was not removed The operative risk is low, as it is now about 4 per cent and probably it is less than this when the operation is performed by a surgeon who is an expert in this field To fail to operate on these patients is to run the risk of long periods of ill health or death in one of the almost inevitable hemolytic crises Furthermore it should be kept in mind that additional disability may result from cholelithiasis which develops in almost 70 per cent of these patients at some time during the course of the disease

There are two points in regard to the operation which should be emphasized especially They are (1) at the time of the operation care should be taken to explore the gallbladder region for stones, and (2) a careful search should be made for accessory spleens which, if found should be removed

This latter matter was emphasized originally by Morrison Lederer and Fradkin in 1928 [9] Recently Curtis and Movitz have made a comprehensive study of the significance of accessory spleens[30] They report that previously accessory spleens were said to occur in 10 to 35 per cent of all patients at necropsy and at operations on patients for splenic disease in 20 to 44 per cent In the 178 patients studied by Curtis and Movitz, the operation having been performed in each instance for various splenic diseases accessory spleens were found in 56 or 31 4 per cent The greatest incidence was observed in patients of the first decade with congenital hemolytic icterus in whom such an accessory organ was present in 57 1 per cent Forty four per cent were observed in patients of the first decade who were operated upon for primary thrombocytopenic purpura The incidence of accessory spleens decreased with age The number of such organs varied in different patients from 1 to 10 26 patients presented only one accessory Of 131 accessory spleens occurring in 56 patients the distribution was as follows, expressed in percentages hilus of the spleen 54 2 pedicle of the spleen 25 1, omentum 12 2 retroperitoneum 6 1 splenocolic ligament 1 5 and bowel mesentery 0 75 It is important to note that, when an accessory spleen does occur in more than one location the hilus of the spleen always constitutes one of these

Following splenectomy in patients with congenital hemolytic icterus the serum bilirubin and urobilin excretion return promptly to normal levels The red blood cell count rises and the number of reticulocytes in the circulating blood returns to normal These changes begin within a few hours after the operation and are complete within a few weeks According to Thompson[31] the spherocytes persist with their associated fragility changes for many years after splenectomy This observer states that he has observed spherocytes to the extent of 14 per cent of all the circulating erythrocytes in a patient 16 years after splenectomy It is the opinion of Vaughan[32] that fragility invariably persists following splenectomy but that spherocytosis disappears in about one half of the patients

those responsible for the anemia in malaria and in Bartinellosis animal poisons as snake venom vegetable poisons as the fava bean and extensive burns

Drugs and Chemicals which May Cause Hemolytic Anemia

The Sulfonamide Drugs — Coincident with the introduction of these drugs into clinical medicine it was discovered that a hemolytic anemia may be associated with their use It has been estimated[34] for example that about 4 per cent of patients who received sulfanilamide therapy developed hemolytic anemia Such an anemia has been reported in association with the use of sulfapyridine[35] sulfathiazole[36] sulfadiazine[37] and promine[38] As far as I know no cases have been known to occur following the use of sulfaguanidine or sulfasuxadine In my own experience this variety of anemia has been rare and considering the widespread use of these drugs it must be only a small per cent of the patients who suffer from this complication Nevertheless the importance of such a complication must be kept in mind for it may terminate fatally Its seriousness is shown by the report of Fox and Ottenberg[39] who observed a group of 9 cases in which there were 6 deaths

The Blood in Lead Poisoning — This subject will not be discussed in detail here but is mentioned only for the sake of completeness as this topic is presented elsewhere in this system It should be mentioned however that if in association with a mild to moderate normochromic normocytic anemia there is stippling of the red blood cells then the possibility that lead may be the responsible etiological factor should be given careful consideration The most commonly accepted view is that the anemia of lead poisoning results from an increased destruction of erythrocytes in the circulating blood[40] It is considered by some[40] that lead unites with the inorganic phosphate of the erythrocyte to make it more brittle and therefore more easily destroyed While increased blood destruction is the chief cause of the anemia in lead poisoning in my opinion it has been held by others[41] that lead inhibits the synthesis of hemoglobin by preventing the incorporation of iron into the photoporphyrin nucleus

Phenylhydrazine and Acetylphenylhydrazine — It has long been known[1] that both phenylhydrazine hydrochloride and acetylphenylhydrazine may produce a severe anemia in man or animals by an increased destruction of red blood cells This action has been utilized in the past to treat patients with polycythemia rubra vera but it has been supplanted by the more efficient radioactive phosphorus or spray roentgen ray therapy Both types of phenylhydrazine are known to be toxic and hence when employed therapeutically considerable care must be used in order not to produce an anemia

Acetanilid — It is recognized that chronic acetanilid poisoning may produce a hemolytic anemia of considerable extent[42] The peculiar cyanosis which may

initial dose of 12 grams of sodium bicarbonate to be followed by 4 teaspoonfuls daily to such patients If the emergency is such that rapid alkalinization is indicated, this may be accomplished by the administration of 500 c c of one sixth molar solution of sodium lactate intravenously, the same amount of 2 to 4 per cent solution of sodium bicarbonate or 200 c c of a 2 5 to 3 0 per cent solution of sodium citrate All of these solutions can be obtained in sterile containers ready for immediate use

ACQUIRED HEMOLYTIC ANEMIA

Introduction

The acquired hemolytic anemias may be observed in the acute subacute and chronic forms Dameshek and Schwartz[15] include all types of acquired hemolytic anemias in the following classification

I Secondary to known causes (bacterial infections chemicals, toxic", pregnancy, etc)

II Symptomatic in association with certain usually malignant diseases, such as lymphatic leukemia, Hodgkin s disease carcinomatosis

III Of unknown cause with or without hemolysins in the serum

(a) Chronic with or without crisis

(b) Subacute

(c) Acute

(d) Acute fulminating often with hemoglobinuria

Secondary Hemolytic Anemia (Acute and Chronic)

It is known that an acute hemolytic anemia may be produced by a wide variety of etiological agents including drugs animal poisons, bacteria and protozoal organisms and in association with burns Such an anemia may be classified as acute subacute or chronic depending upon the intensity and duration of the action of the hemolytic agent If the condition is acute the clinical manifestations resemble those which are described under the heading of Acute Idiopathic Acquired Hemolytic Anemia on a following page if the causative agents act more mildly and for a longer period of time the clinical conditions are similar to those described under the heading of Subacute or Chronic Hemolytic Anemia Acute and chronic hemolytic anemia due to infection is discussed in detail under the section of anemia due to infection

Among the more important drugs which may be responsible for this type of anemia are the sulfonamides, lead, phenylhydrazine, acetanilid arseniuretted hydrogen and dinitrophenol Other causes are protozoan organisms such as

entirely clear The symptoms of this disorder develop abruptly and consist of chills fever prostration restlessness and vomiting There is a hemoglobinuria and a rapidly developing hemolytic anemia followed by a definite jaundice It has been suggested that the condition is due to the *Plasmodium falciparum* or that it might arise as a result of a previous sensitization by the same organism[49]

Bartonelliasis — This disease is due to a specific organism *Bartonella bacilliformis* which probably is transmitted by a sand fly It produces in man a condition characterized by an acute febrile anemic stage designated as Oroya fever which is followed usually within several weeks by a nodular eruption known as verruga peruviana The malady appears to be limited to the Andes mountains *in Peru and other South American countries*

The blood picture is typical of that due to increased erythrocyte destruction with an associated leukocytosis The red blood cell count may fall to 1 0 millions per cubic millimeter within a few days in the acute cases The liver spleen and lymph nodes often are found to be enlarged

Hemolytic Anemia Due to Other Causes

Snake Venom — It has been known for many years that the venom of certain poisonous snakes will produce among other toxic effects hemolytic anemia It has been shown recently by Bethell and Bleyl[50] that a microspherocytosis and hemolytic anemia will follow the injection into dogs of the venom of *Crotalus atrox* (Texas diamond back rattlesnake) By repeated administration of small amounts of venom to dogs they were able to cause the development of a hemolytic anemia accompanied by hyperbilirubinemia and reticulocytosis

Favism — Favism is a condition characterized by a rapidly developing hemolytic anemia hemoglobinuria and jaundice due to the ingestion of the seeds or inhalation of the pollen of the flowers of *Vicia fava* commonly known as the fava or broad bean Only an occasional case has been reported in the United States and at present the condition is limited largely to the inhabitants of the island of Sardinia although it has been observed on the mainland of Italy and in Sicily[51] Within a very short time after exposure to this agent the red blood cell count may fall to 1 or 2 0 millions per cubic millimeter and some *report that the color index is reduced to below 1 0 There is a marked leukocytosis* during the first 6 to 7 days of the attack

Hemolytic Anemia Due to Burns — It is known that a hemolytic anemia *may be associated with extensive burns and in some cases there may be a hemo*globinuria In the Coconut Grove disaster of Boston in November 1942 it was observed that in 39 living patients who were admitted to the Massachusetts General Hospital 9 developed a hemoglobinuria and it was thought that at least 8 and perhaps all were due to the burns per se More recently information

accompany the excessive ingestion of this drug is a valuable diagnostic sign, but unfortunately it is not always present It is of interest to note that the splenomegaly which may be present in some patients for years, is rapidly reversible when the source of the poisoning is removed

Arseniuretted Hydrogen — This substance is known to be toxic and among its effects is the production of a severe hemolytic anemia with jaundice It is known to cause such an anemia in persons exposed to the fumes from storage batteries made from a lead antimony alloy which is contaminated by arsenic[44] and in workers with fish fertilizer which had been sprayed with sulphuric acid contaminated with arsenic[45]

Nitroaniline Compounds — During World War I it was discovered that trinitrotoluene[46] could be responsible for a hemolytic anemia[46] and that dinitrobenzene and other nitroaniline compounds may account for severe grades of jaundice and anemia of a hemolytic type[47]

Hemolytic Anemia Due to Protozoa

Malaria — The most important organisms of this class causing hemolytic anemia are the plasmodium of malaria, and the bartonella bacilliformis which is the cause of bartonellosis or Oroya fever Undoubtedly malaria is the most common cause of a hemolytic anemia throughout the world It is generally accepted that the anemia is due primarily to an increased rate of destruction of the erythrocytes which results from the presence of the parasite intracellularly Studies have shown that when a malaria infection is controlled by therapy, the reticulocytes which are usually less than 1 0 per cent during the active untreated phase of the disease increase within a day or so until they reach 8 to 10 per cent This observation has been interpreted as (1) indicating that the bone marrow is depressed by the action of the malarial parasite and the anemia while predominantly due to hemolysis may in part be attributed to depression of the erythroblastic elements in the bone marrow or (2) it may be explained on the basis that the reticulocytes for some unknown reason are infected selectively by the parasite Of the two views probably the latter one is the more likely

In about two thirds of the cases the anemia is of the macrocytic or normocytic type, in about 16 per cent it is of the simple microcytic type and in 13 per cent of the hypochromic variety[48] The red blood cell count usually is in the vicinity of 3 0 millions per cubic millimeter and the hemoglobin averages about 60 per cent (9 36 grams) The white blood cell count usually is normal or below normal In about one third of the patients the leukocyte count is below 5 000 per cubic millimeter and it may be as low as 2 000 per cubic millimeter

Blackwater Fever — In this condition there is an acute hemolytic anemia in association with a malarial infection, although its relation to the latter is not

rapidity While the anemia most commonly is normochromic and normocytic it may be macrocytic or microcytic the actual volume of the cells depending on the number of spherocytes which are present and this in turn is proportional to the rapidity of the development of the anemia

Urine and Stools

The urine is dark but there is an absence of bilirubin and hence the deep color must be attributed to other urinary pigments It is known that urobilin and urobilinogen usually are present in increased amounts In some patients in whom there is an exceedingly rapid destruction of blood there is a hemoglobinuria and hence the condition may be regarded as a variety of paroxysmal hemoglobinuria

The stools are highly colored and there is an output of 10 to 20 times the amount of pigment in excess of normal

The blood serum has a deep color due to an increased amount of bilirubin as a result the icterus index is usually between 25 and 35 units and the actual bilirubin content of the serum is between 1 5 and 8 milligrams or higher per 100 c c. The bilirubin reaction is the indirect van den Bergh type

Treatment

In the treatment of a patient with this type of anemia there are two questions of major importance to decide namely (1) should blood transfusions be given and (2) is an emergency splenectomy advisable and urgent In regard to the blood transfusions it is my opinion that if the patient is in a state of shock with a red blood cell count in the vicinity of 1 0 to 1 5 per cubic millimeter several transfusions of approximately 500 c c each should be given This is provided that blood can be obtained from donors which appear to match perfectly The blood should be given slowly not faster than 500 c c in 3 hours it should be diluted with equal parts of 5 per cent dextrose solution and the patient should have been given a sufficient amount of sodium bicarbonate to alkalinize the urine

The advisability of splenectomy is a difficult one to decide but it should be considered always although Dameshek[85] concedes that it carries with it a mortality rate of 40 per cent It is his opinion with which I agree that with careful management this high mortality rate should be lowered Furthermore once the patient has shown that a favorable response is not to follow treatment with blood transfusions splenectomy offers the best chance for recovery despite its high mortality rate Moreover if several blood transfusions are not of benefit additional ones are not likely to be of further help

bearing on the effects of thermal burns has been made available by the studies of Shen and Ham[5] They conclude that there may be an increased destruction of erythrocytes following burns due to increased osmotic fragility which results from the conversion of the normal biconcave erythrocytes to the more nearly spherical forms It is their belief that in thermal burns a significant number of erythrocytes may be destroyed by heat probably depending on the temperature attained by the blood the duration of the heating and the volume of the blood subjected to these conditions

Other possibilities which may contribute to the development of anemia in burns is the inhalation of poisonous gases[53] and intestinal hemorrhages[54] As in the studies quoted observations demonstrated that increased hemolysis of blood even to the point of producing hemoglobinuria is caused by extensive burns it is to be inferred that such alterations in the blood could easily account for varying degrees of anemia

Acute Acquired Idiopathic Hemolytic Anemia

Definition and General Statement

Synonyms —Acute hemolytic jaundice of the acquired type Lederers anemia

This condition may be defined as an acute subacute or fulminating type of anemia resulting from an increased destruction of red blood cells which is not due to the well recognized causes It is characterized by an increased excretion of urobilin in the stools an excess of bilirubin in the circulating blood signs of active formation of red blood cells and usually a normocytic normochromic anemia of varying severity In the opinion of some[15] it arises from the action of isohemolysins which cause increased spherocity and consequently a greater fragility of the erythrocytes Blood transfusions often are helpful and some patients have been reported as cured by splenectomy Before concluding that any given patient is suffering from this type of acute hemolytic anemia one must be careful (1) to exclude all known causes of hemolytic anemia ( ) to be convinced that the condition is not an exacerbation of congenital hemolytic jaundice (3) and finally that it is not identified with either the paroxysmal or nocturnal type of hemoglobinuria

Changes in the Blood

In many cases there is a profound anemia with a red blood cell count which varies from 1 0 to 1 5 millions per cubic millimeter and a hemoglobin which is between 25 and 35 per cent of normal The anemia may develop with amazing

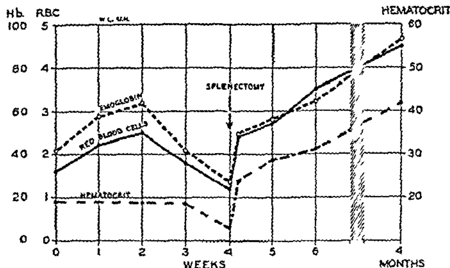


FIG 2 The hemoglobin is expressed in per cent of normal which arbitrarily is set at 15 6 per 100 c c as 100 per cent The red blood cells are in millions per cubic millimeter and the hematocrit in percentage This patient had the classical manifestations of an acquired hemolytic anemia with an ultimate return of the blood to normal following splenectomy For a period of 4 weeks however the patient was observed with no other treatment than one blood transfusion Following this the anemia became progressively worse the hemoglobin finally reaching 28 per cent the red blood cell count 1 2 million per cubic millimeter and the hematocrit 8 per cent Operation then was deemed advisable and urgent The patient was last seen 10 months after the operation at which time the red blood cells were 4 6 million per cubic millimeter hemoglobin 83 per cent (12 5 grams per 100 c c of blood) and the hematocrit 42 5 per cent Approximately the same number of microspherocytes were present in the circulating blood as there were prior to the splenectomy The patient was in good health and had no complaints

of some weeks observation in which there is *no* evidence of improvement I have reached this conclusion for the following two reasons first and most important there is evidence to indicate that about two-thirds of our patients show material objective improvement following splenectomy and some have had a complete restoration of health with a return of the blood entirely to normal It should be recognized that in some of our patients the time has undoubtedly been too short upon which to base a definitive opinion for in some instances the interval since splenectomy has been less than one year Additional time is necessary therefore in order to evaluate this phase of the problem adequately but at least our preliminary observations are encouraging The second reason for considering splenectomy in such patients is the lack of any other type of treatment which is effective and the knowledge that spontaneous recovery with complete return of the blood to normal does not occur frequently in such patients

Chronic Acquired Idiopathic Hemolytic Anemia

Differentiation from the Other Types

If it is well established that the patient is suffering from a chronic hemolytic anemia, and if the secondary types due to chemicals infections and other causes can be eliminated, then one is confronted with the problem of differentiating between the chronic congenital anemia and the acquired variety This is of importance chiefly because the results from splenectomy are more satisfactory in the congenital than the acquired type In fact, some observers will not concede that removal of the spleen is ever helpful in any patient with the acquired type While I do not agree with this nevertheless it is true that the number of patients who recover or show some definite evidence of improvement is less in the acquired than in the congenital variety

From my own experience I would say that the only absolutely definite and convincing evidence of congenital hemolytic anemia is the demonstrated presence of another case in the blood relatives The fact that examination of other available members of the family fails to reveal evidence of hemolytic anemia however, does not eliminate the congenital variety from consideration although it is strong evidence against it

The following additional considerations are helpful but not conclusive in differentiating between the two varieties

1 The active manifestations usually appear in infancy or childhood in the congenital type and often at a much later age in the acquired variety

2 An enlarged liver or lymph nodes or both are present frequently in the acquired variety such changes are much less common in the congenital type

3 Microspherocytes are present in all cases with the congenital variety, but such cells are not so common in the acquired type Furthermore in the former there is almost without exception an increased fragility, whereas in the acquired variety this is present in only about 40 per cent of the patients

4 The leukocyte count has a tendency to be normal or slightly elevated in the congenital variety but there is often a leukopenia in the acquired types Furthermore in the latter there are not infrequently a few abnormal lymphocytes and monocytes

5 It has been my experience that splenectomy is practically always successful in patients with congenital hemolytic anemia (Fig 2) and I have not hesitated to recommend that the procedure be carried out promptly once the diagnosis has been established That splenectomy produces less favorable results in patients with the acquired type is the opinion of all observers but there is a lack of agreement concerning the exact number of patients who are not benefited by such an operation In my opinion such an operation is justified after a period

The erythrocytes may have an increased mean corpuscular volume or there may be a pseudomacrocytosis as indicated by an average volume of the erythrocytes which is greater than normal and a mean diameter which is less than normal This can occur only when spherical erythrocytes are present in large numbers The color index is almost always 1 0 or more and the mean corpuscular hemoglobin concentration is usually above 30 per cent

Treatment and Prognosis

The therapy and outlook in any given case depends largely on the underlying cause of the hemolytic anemia In many cases it is neoplastic in nature and hence ultimately the outlook is hopeless It should be remembered however that such an anemia might be due to a benign condition such as an ovarian cyst and its removal may be followed by a complete restoration of the blood to normal

Hemoglobinuria

Definition —This condition may be defined as a state characterized by the presence of free hemoglobin and the absence of intact red blood cells in the urine Such a finding always is indicative of excessive intravascular destruction of red blood cells which exceeds the capacity of the reticuloendothelial system to convert the normal amount of hemoglobin thus liberated into bilirubin Hence hemoglobin is excreted into the urine when the amount present in the circulating plasma exceeds its renal threshold

Classification

The grouping of these conditions into two principal types of (1) hemoglobinuria and (2) paroxysmal hemoglobinuria is obvious and serves a useful purpose It should be emphasized that the first group consists of the same subgroups as those of the hemolytic anemias of which the principal ones are those due to chemical agents isoagglutinins autoagglutinins various parasites such as the malarial organism and the one causing Oroya fever

The only difference between the hemolytic anemia as caused by these agents and hemoglobinuria is the speed of destruction of the red blood cells In the latter condition the erythrocytes are destroyed so rapidly that an excessive amount of hemoglobin is liberated and this is eliminated in the urine hence producing the hemoglobinuria In hemolytic anemia the same process occurs but as it is much slower the free hemoglobin never reaches the level in the blood stream where it exceeds the threshold of the kidney and hemoglobinuria does not occur

Additional information which has a bearing on this is desirable however, and my present form of management is to place a patient under continued observation for several weeks, giving blood transfusions if necessary If encouraging signs of improvement do not appear within 4 to 6 weeks, splenectomy is considered seriously

SYMPTOMATIC HEMOLYTIC ANEMIA

Introduction

Definition — This condition may be defined as a syndrome which presents a picture similar to familial hemolytic jaundice including the changes in the blood and splenomegaly, but showing a definite etiological relationship to some underlying disease which is sometimes, but not always, of a neoplastic nature such as Hodgkin s disease generalized carcinomatosis and others The subject has been reviewed fully by Waugh[56] Watson[57] and Singer and Dameshek[58]

That an anemia of the hemolytic variety may be observed sometimes in association with these conditions is of importance for two reasons namely, (1) because the recognition of the cause might prevent an unnecessary splenectomy in a patient who was thought to be suffering from an acquired or familial hemolytic anemia, and (2) in certain cases where the underlying condition is remedial such as a dermoid cyst, it may present a much more favorable outlook

Etiology

The condition has been observed in association with dermoid cyst (teratoma) of the ovary carcinoma with metastases to the bone marrow, lymphosarcoma Hodgkin s disease leukemia in liver disease and in infectious diseases including streptococcic and staphylococcic infections tuberculosis and those due to anaerobic organisms such as *B welchii*

Blood Changes

In most instances spherocytosis with increased fragility can be demonstrated by careful examination As in all cases of hemolytic anemia there are evidences of increased regenerative activity on the part of the marrow This is indicated by an increased number of reticulocytes polymorphonuclear leukocytes immature granulocytes and platelets in the circulating blood Nucleated red blood cells and cells showing polychromatophilia are characteristically present The bone marrow in such patients usually shows an extreme hyperplasia especially of the red blood cell forming elements

therapy the autohemolysin may disappear from the blood and the serological reactions for syphilis become negative

March Hemoglobinuria

Definition — The name March hemoglobinuria is based on the observation that hemoglobinuria is observed sometimes in soldiers or other young males following prolonged marches or after other forms of strenuous exertion

Etiology

Although the condition previously has been considered as rare the fact that Blumgart and Gilligan[39] observed 3 cases in a relatively short period and subsequently other examples in otherwise healthy athletes after strenuous exercise suggests that the incidence of the disorder is much greater than had been previously supposed It has been shown by these authors that a hemoglobinemia sometimes accompanied by a hemoglobinuria occurs in a large proportion of cross country and marathon runners Furthermore it may develop even following short walks or runs in some persons on account of postural or mechanical factors such as produced by a kyphotic position

Symptoms and Signs

Ordinarily there are no symptoms or signs of the condition and it is considered to be benign It is of importance only because of the possible confusion with some other more serious type of paroxysmal hemoglobinuria or with hematuria It appears to be good judgment however for persons in whom this phenomenon occurs to refrain from strenuous exertion

It is estimated that only from 6 to 40 c c of blood is destroyed intravascularly during an attack and that less than 10 per cent of the hemoglobin thus freed in the plasma appears in the urine The hematocrit and the red blood cell counts are normal at all times The urine is pink red or black depending on the amount of hemoglobin which is present Such coloration must be differentiated from hematuria porphyrinuria in which the color is due to urofuchsin myohemoglobinuria and from the red color due to beets phenophthalein or neoprontosil. If the benzidine or guaiac test is positive and there are no red blood cells present then the pigmentation must be due to either free hemoglobin or myohemoglobin The diagnosis of hemoglobinuria may be confirmed by a spectroscopic examination It should be kept in mind that both an acute nephritis and an infarct of the kidney also can produce hemoglobinuria, but in such conditions there is an absence of hemoglobinemia

The paroxysmal hemoglobinurias are of such a nature as indicated by the intermittency of the hemoglobinuria that they should be placed in a separate division These conditions may be classified as follows

I Cold hemoglobinuria
II March hemoglobinuria
III Nocturnal hemoglobinuria (Marchiafava Micheli type)
IV Allergic hemoglobinuria (Favism)

Cold Hemoglobinuria

Definition — Cold hemoglobinuria may be defined as a condition characterized by the transient appearance of hemoglobinuria associated with exposure to cold which apparently causes an autohemolysin in the blood to unite with the erythrocytes It is of interest to note that almost all of these patients have clinical evidence of syphilis either acquired or congenital

Tests

There are two tests for this condition which are useful One is the Rosenbach test which consists simply of placing the hands or feet in cold water for 10 or 15 minutes and observing if hemoglobinuria is produced The other is the Landsteiner Donath reaction which may be described as follows The patient's serum and cells are separated and the latter are prepared in a 10 to 15 per cent suspension in saline solution Equal parts of the patient s serum and fresh guinea pig complement are added to the suspension of erythrocytes and this is chilled for 30 minutes Apparently the cooling permits the absorption of lysin by the red blood cells This is demonstrated because following the exposure to lowered temperature when the mixture is incubated at 37° C for 30 minutes hemolysis of the patient s red blood cells results Furthermore the red blood cells of a normal person can be substituted in the reaction and the serum from the patient with the cold paroxysmal hemoglobinuria will produce the same hemolysis under the conditions outlined This demonstrates that the abnormality is not concerned with the erythrocytes but that the lysin must be in the patient s serum

During an attack there may be a precipitous fall in the red blood cell count to 2 5 or 3 0 million per cubic millimeter indicating an almost incredulous destruction of erythrocytes

Treatment

The only therapy which is of value is the prevention of exposures to cold and the treatment of the syphilitic condition which almost invariably is present Untreated cases may continue with exacerbations for years With anti syphilitic

to hypotonic salt solutions The blood bilirubin usually is moderately elevated but it may vary anywhere between 0 8 and 3 6 milligrams per 100 c c of blood

Prognosis and Treatment

There is no satisfactory treatment of this condition The administration of alkalies and splenectomy is ineffective Blood transfusions may be followed by transient evidence of increased hemolysis but following this there may be a significant decrease in the hemolytic process for a period of several days to a week The only measures of possible benefit are a well balanced diet a limitation of activity and the avoidance of infection

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Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava Micheli Syndrome)

Definition — This is an exceedingly rare form of chronic hemolytic anemia characterized by the symptoms and signs of chronic red blood cell destruction associated with attacks of hemoglobinuria which occur chiefly at night It was described by Marchiafava and Nazari in 1911[60] and more completely by Micheli in 1931[61]

Etiology

The syndrome is characterized by a continuous intravascular hemolysis and hemoglobinemia with an intensification of the process during sleep, which results in the appearance of hemoglobin in the urine when in this state It has been concluded by Ham[6] after a comprehensive study of 5 cases that the abnormality resides in the red blood cells He observed that the nocturnal hemoglobinuria is associated with sleep and not with posture the ingestion of food or liquid or the time of day or night that sleep occurred It is his belief that the greatest degree of hemolysis was present in association with diminished alkalinity of the blood, especially in regions of the body subject to stasis such as the spleen

Symptoms and Signs

The manifestations are those of a chronic hemolytic anemia associated with transient hemoglobinuria and characterized by the passage of red urine during sleep Vague abdominal cramps backache malaise and a dull headache commonly are present in these patients

Since the anemia may become severe, as indicated by an erythrocyte count of below 2 0 million per cubic millimeter the symptoms common to all anemias such as ease of fatigue weakness dyspnea and palpitation may be pronounced The physical signs are pallor with a mild icterus and sometimes a barely palpable liver and spleen

Blood Changes

There is a moderate to severe normochromic normocytic anemia or macrocytic anemia with a leukopenia and a reticulocytosis In Ham's cases[6] the mean corpuscular volume varied from 89 to 131 cubic microns and the mean corpuscular hemoglobin concentration from 29 to 31 per cent The white blood cell count fluctuated between 3 330 and 6 000 per cubic millimeter with a normal differential and blood platelet count There was no increased fragility of the red blood cells

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CHRONIC CONGESTIVE SPLENOMEGALY (BANTI'S SYNDROME)

Synonyms — Splenic anemia fibrocongestive splenomegaly

Definition — This condition is a syndrome usually resulting from a circulatory disturbance of the spleen associated with a hypertension of the splenic vein It is characterized by chronicity hemorrhages from the upper gastrointestinal tract splenomegaly a hypochromic anemia leukopenia frequently thrombopenia evidence of a collateral circulation between the portal and peripheral venous circulation and by certain constant anatomical changes in the spleen

History

Although the first description of the disease is accredited to Banti[1] in 1882 he quotes Woillez as describing a progressive anemia in association with a large tumor of the spleen and Gretsel[2] as discussing a similar case and introducing the term splenic anemia It is of interest to note that in 1904 Dock and Warthin[4] reported two cases with the syndrome of Banti's disease which they preferred to call splenic anemia In both cases there was calcification and stenosis of the portal vein They concluded their article with the following sentence The two reported cases however may be taken as further evidence in favor of the view that the symptom-complex of splenic anemia represents a group of varying pathological conditions the splenic condition being secondary This opinion entirely agrees with the ideas concerning the nature of the disease as advanced by Thompson[5] in recent years

Etiology and Pathology

Theories Relating to the Cause of the Syndrome

The disease usually appears in the first half of life that is before the age of 35 years but it may be present in infancy or old age Some claim that it is more prevalent in the female sex but statistics dealing with large groups of cases are not in accord with this There is no evidence that heredity plays an important role although more than one case has been known to occur in the same family

It was the original theory of Banti that the condition resulted from the action of some unknown toxic agent acting first on the spleen and then on the liver but this view is no longer tenable

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According to Rousselot[6] the failure to discover an obstructive factor in the other 7 cases is not necessarily a weakness in the hypothesis which considers that splenic hypertension is a cause of Banti s syndrome In his opinion the lack of an apparent cause may be attributed to the technical difficulties involving an operative examination of the portal venous bed away from the splenic hilum particularly behind the head of the pancreas

Ravenna[7] is not in accord with Thompson s belief that evidence of obstruction of the flow from the splenic vein is invariably present In his opinion all of the clinical and pathological signs of splenic congestion can be observed in patients in the absence of an obstructive factor in the portal vessels He believes that there may be changes in the malphigian and other small arteries of the spleen which consist of periarterial hemorrhages and periarterial fibrosis As a result of these changes he assumes that the function of adjusting the intake of blood in the spleen is altered and as a consequence an increased quantity enters that organ which must be discharged through the hepatic resistance under normal conditions Hence the pleen becomes congested and there is an increase in the pressure of the out flowing blood

As an indication of the possible multiple causes which may be responsible for chronic congestive splenomegaly (Banti s syndrome) the following schema showing the possible causes of the condition has been suggested by Ravenna[7]

A Banti s syndrome (of known origin)
- 1 Infective
  - a Syphilis
  - b Leishmaniasis
  - c Schistosomoasos
  - d Malaria
  - e Tuberculosis
- 2 Toxic
  - a Alcohol
  - b Lead
  - c Phosphorus

B Of unknown origin (primary fibrocongestive splenomegaly with cirrhosis)
- 1 With prevailing congestion
- 2 With prevailing fibro is

Pathological Changes in the Spleen

The changes in the spleen in this syndrome are the same regardless of the cause They are follicular atrophy widespread fibrosis of the pulp with distended venous sinuses the characteristic perifollicular hemorrhages diffuse sidero is and siderotic nodules

Recently Thompson[5] has emphasized that in his opinion the syndrome arises as the result of a variety of primary lesions all of which have in common the production of increased pressure in the splenic vein In support of this he cites his observations on the pressure determinations in the splenic vein as measured in a group of these patients at the time of splenectomy He concudes that ' there is no doubt that a splenic vein hypertension of great magnitude, is an important and invariably present factor in this disturbance '

The obstructive factors responsible for the splenic vein hypertension are divided into two groups by Thompson as follows the intrahepatic and the extra hepatic In his opinion there is no difference clinical or hematological, between the congestive splenomegalies resulting from the various types of obstruction The intrahepatic lesion responsible for congestive splenomegaly is cirrhosis of the liver which was present in 68 per cent of all of his cases In the opinion of Thompson[5], when all of the cases of Laennec's cirrhosis are considered about 60 per cent of them will have splenomegaly of the Banti s type and esophageal varices

A large proportion of these patients present the clinical picture of Banti s syndrome, and he believes that many ultimately die of hemorrhage from ruptured esophageal varices In the remaining 40 per cent of the cases of Laen nec s cirrhosis the liver syndrome is observed as there is more injury to the liver parenchyma in these patients He believes that these patients are more likely to succumb to hepatic insufficiency with clinical cholemia Likewise it is concluded by Thompson that, if cirrhosis is not present in a patient with chronic congestive splenomegaly at the time the spleen is observed to be enlarged it will not appear subsequently

Whereas cirrhosis in slightly more than one half of his cases accounted for the hypertension of the splenic vein in the remainder it was attributable to extra hepatic causes The extrahepatic causes responsible for this syndrome may be many and varied in nature Among those which have been mentioned are thrombosis of the portal or splenic veins, compression of these veins by tumors or scars stenosis of the portal vein and possibly, other defects of a developmental nature

A special study of the extrahepatic factors responsible for congestive splenomegaly has been reported by Rousselot[6] In 8 of his 15 cases a definite extra hepatic lesion was found as follows (1) thrombosis of splenic vein (traumatic), (2) thrombosis of splenic vein at junction of portal vein (traumatic), (3) thrombosis of splenic vein (non traumatic) (4) thrombosis of splenic vein (non traumatic) (5) stenosis of portal vein (upper end) just below the liver (6) stenosis of portal vein (lower end) above entrance of splenic vein (7) cavernomatous transformation of portal vein, (8) cavernomatous transformation of junction of portal vein and splenic veins

According to Rousselot[6] the failure to discover an obstructive factor in the other 7 cases is not necessarily a weakness in the hypothesis which considers that splenic hypertension is a cause of Banti s syndrome In his opinion the lack of an apparent cause may be attributed to the technical difficulties involving an operative examination of the portal venous bed away from the splenic hilum particularly behind the head of the pancreas

Ravenna[7] is not in accord with Thompson s belief that evidence of obstruction of the flow from the splenic vein is invariably present In his opinion all of the *clinical and pathological signs of splenic congestion can be observed in patients in* the absence of an obstructive factor in the portal vessels He believes that there may be changes in the malphigian and other small arteries of the spleen which consist of periarterial hemorrhages and periarterial fibrosis As a result of these changes he assumes that the function of adjusting the intake of blood in the spleen is altered and as a consequence an increased quantity enters that organ which must be discharged through the hepatic resistance under normal conditions Hence the pleen becomes congested and there is an increase in the pressure of the out flowing blood

As an indication of the possible multiple causes which may be responsible for chronic congestive splenomegaly (Banti s syndrome) the following schema showing the possible causes of the condition has been uggested by Ravenna[7]

A Banti s syndrome (of known origin)
 1 Infective
  a Syphilis
  b Leishmaniasis
  c Schistosomoasos
  d Malaria
  e Tuberculosis
  Toxic
  a Alcohol
  b Lead
  c Phosphorus
B Of unknown origin (primary fibrocongestive splenomegaly with cirrhosis)
 1 With prevailing congestion
 2 With prevailing fibro is

Pathological Changes in the Spleen

The changes in the spleen in this syndrome are the same regardless of the cause They are follicular atrophy widespread fibrosis of the pulp with distended venous sinuses the characteristic perifollicular hemorrhages diffuse siderosis and siderotic nodules

Symptoms and Signs

The onset of the disease is almost always insidious, and undoubtedly in many cases the condition has been present for a period of years before the clinical manifestations appear The most common chief complaints are weakness associated with the anemia a mass and discomfort in the left side of the abdomen and hematemesis In general it may be said that the symptoms center about three changes in the body namely, the anemia the enlarged spleen and bleeding from the gastrointestinal tract

The symptoms associated with the anemia are the usual ones of weakness ease of fatigue pallor dyspnea and palpitation Ordinarily they are not pronounced unless the anemia is unusually severe this usually results from repeated hematemeses Gastrointestinal hemorrhages which manifest themselves by hematemesis or tarry stools or both, occur in about one half of the cases They are known to be associated with portal congestion and the formation of a collateral circulation in the region of the lower end of the esophagus The loss of blood may be considerable and result in the development of a severe anemia or death may occur occasionally from acute hemorrhage

Pain in the upper abdomen is not uncommon but it is usually not a prominent complaint and the patient may not mention it unless questioned specifically The pain in the region of the spleen may be associated with perisplenitis but such a complication is rare The discomfort in the upper left quadrant of the abdomen most frequently is due to the dragging weight of the grossly enlarged spleen Occasionally the pain is in the upper right quadrant due to the hepatomegaly The spleen in most instances is moderately enlarged usually weighing from 400 to 2 000 grams but it may reach 3 000 grams and extend to below the umbilicus The liver is enlarged in about one third of the cases but in most instances the edge is barely palpable at the right coastal margin In my experience it is not common to observe a liver which is greatly enlarged Ascites is present as a result of the cirrhosis of the liver in one third of the cases In my opinion this complication is not present unless it is secondary to cirrhosis of the liver but all observers are not in accord with this Definite jaundice is rare in this condition but it does occur A curious sallow brownish pigmentation may be observed in some patients which is similar to that seen in Addison s disease

Changes in the Blood

Before considering the changes which occur in the blood it should be emphasized that there are two possible causes for the anemia in this condition The one which is the most common is bleeding either acute or chronic or both from esophageal varices This is the common cause and results in the develop-

ment of a hypochromic anemia The other cause is associated with the wide spread liver disease which results in an interference with the storage of the erythrocyte maturing factor and consequently a macrocytic anemia may appear From a theoretical standpoint, then a variable type of anemia may be present in Banti s disease depending on which one of the two mechanisms predominate It is known from experience however that the most commonly encountered one is a normochromic or hypochromic normocytic anemia which ordinarily is moderate in severity, with a red blood cell count averaging about 3 0 to 3 5 millions per cubic millimeter If gastrointestinal bleeding is profuse or mild and protracted then the anemia may become the hypochromic variety

One of the most constant features of the blood picture is the ever present leukopenia The white blood cell count usually is below 5 000 per cubic millimeter and the reduction commonly affects all varieties of the white blood cells

The blood platelets may be less than 100 000 per cubic millimeter and this is associated sometimes with an abnormal tendency to bleed Ordinarily however there is no change in the bleeding or clotting time in this condition

Course of the Disease and Prognosis

This condition may pursue a chronic course extending over years without producing disabling symptoms especially in young persons in whom it most commonly develops At any time however there is a possibility that gastrointestinal bleeding may occur suddenly with hematemesis or tarry stools which may lead to a severe hypochromic anemia or death from hemorrhage In other patients evidences of liver insufficiency or ascites may appear or the signs of portal thrombosis may develop In general while it can be said that often these patients live for years and many lead a fairly normal existence it is impossible to predict when changes in the patient s condition may occur abruptly with partial or complete disability or death from acute hemorrhage liver insufficiency or intercurrent infection

Treatment

The treatment of this condition is concerned chiefly with the management of the anemia and a consideration of the advisability of splenectomy Following severe bleeding blood transfusions may be necessary in order to save life and to expedite the return of the blood to normal If a hypochromic anemia develops as the result of the loss of blood then adequate doses of iron should be given in the form of ferrous sulphate 0 3 to 0 6 grams 3 times daily When the anemia is of the macrocytic type which may be due to an associated cirrhosis of the

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liver then antipernicious anemia therapy in the form of liver extract, injected intramuscularly is indicated

Splenectomy as a Therapeutic Measure

For many years there has been a difference of opinion concerning the advisability of splenectomy in this syndrome After considering a fairly large group of patients at the University of Michigan Hospital, about one half of whom had been subjected to a splenectomy and the other half had not, I can see no advantage from the operation In the group with splenectomy the duration of life, the tendency to hemorrhage and the degree of disability has been approximately the same as in those in whom the operation had not been done The argument that early operation might avert injury to the liver a belief which seems to have become deeply ingrained in the minds of many medical men is no longer valid This is because as Thompson[5] has pointed out cirrhosis of the liver is the primary cause of the condition in 68 per cent of the cases This infers that in the remaining group in which there is no cirrhosis the condition will never appear regardless of whether or not the spleen is removed Certainly there are cases in which cirrhosis continues to progress leading to a fatal termination at varying intervals following splenectomy Furthermore it should be kept in mind that in the past the removal of the spleen has been associated with a mortality rate of 20 to 30 per cent Death usually has resulted from peritonitis, intraperitoneal hemorrhage liver insufficiency or mesenteric thrombosis

Splenectomy in my opinion is not indicated in these patients because the possible benefits do not warrant the risk of the operation It is true that such an operation may afford a certain measure of relief from portal congestion by reducing the blood flow from the portal vein Also further development of a collateral circulation may be favored at the site of the raw area left by the removal of the spleen An additional relief welcomed by some patients is that afforded by eliminating the dragging sensation due to the grossly enlarged spleen

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that the condition is an acute uniformly rapidly fatal condition of adolescents and young adults which is associated with a high fever a rather sudden development of the anemia without evidence of regeneraton of the erythrocytes and at necropsy the outstanding feature is an extensive fatty degeneration of the bone marrow A complete bibliography to 1911 is given by Hirschfield[6] Sheard[7] in his monograph has covered the literature to 1923 and discovered that 125 cases were reported up to that time

In 1934 Thompson Richter and Edsall[8] reevaluated the information concerning the disease and made an important contribution in that the bone marrow was recognized as actually hyperplastic with signs of active regeneration of the erythrocytes in the circulating blood in some patients with the classical clinical picture of the disease

Important landmarks in the development of our knowledge concerning secondary aplastic anemia are as follows It was noted that the condition could be secondary to benzol by Santesson (1897) It was Selling who made the first experimental studies on this subject[9] In 1905 Heineke noted the deleterious effect of the roentgen rays on the blood but it was not until 1914–1915 that Gavazzeni and Minelli[10] reported the first clear-cut case in which there was evidence of an aplastic anemia following exposure to this agent Other publications have indicated also that roentgen rays[11] radium[12] and radioactive materials[13] may be responsible for the typical picture of aplastic anemia

Although Evans[14] had reported the untoward effect of arsenic in the form of salvarsan on the blood of patients it was Moore and Foley[15] to whom credit should be accorded for having first described a case of aplastic anemia which developed following the use of this drug

The first example of injury to the hematopoietic elements by gold therapy was reported by Weil[16] in 1931 but in this patient the condition was one of thrombocytopenic purpura Cases of aplastic anemia following the use of this therapeutic agent were reported first in 1931 by several French observers[17, 18] A case of aplastic anemia following the administration of gold sodium thiosulphate for the treatment of lupus erythematosis was observed in 1931 and reported in 1933 by Dameshek[19]

Idiopathic Aplastic Anemia

Synonyms — Refractory anemia aleukia hemorrhagica panmyelophthisis hypoplastic anemia

Definition — This condition may be defined as a fatal acute or subacute normocytic normochromic anemia due to hypocellularity of the bone marrow The three most important clinical features are those associated with the anemia the ulcerative lesions on the mucous membranes secondary to the granulocyto-

REFRACTORY ANEMIAS

Classification

In an attempt to classify a group of blood disorders which do not seem to fit into any category the term refractory anemia as used by Bomford and Rhoads[1] has been employed to designate a certain group of anemias in which there are a number of subdivisions The only criteria adhered to in the selection of the anemias to be included in this division have been (1) the fact that they are not benefited by any treatment except blood transfusions and (2) there is no causal or secondary relationship to any recognizable disease such as tuberculosis, nephritis cirrhosis of the liver sepsis lymphogranuloma, subacute bacterial endocarditis and any other known disease the nature of which is known For convenience sake, however the secondary aplastic anemias are included in this section, (3) the anemia is almost always of the normocytic, normochromic type and usually is associated with leukopenia and thrombopenia

It is recognized that such a classification is arbitrary and necessarily a purely tentative one but it at least affords a convenient and temporary method of grouping certain anemias which is helpful The suggested classification of the refractory anemias and closely allied states is as follows

I Refractory anemias
  (a) Idiopathic aplastic anemia
  (b) Atypical aplastic anemia
II Secondary aplastic anemia
III Osteosclerosis
IV Albers Schonberg disease
V Myelophthisic anemias

History

The earliest reported case of aplastic anemia is the frequently cited one observed by Ehrlich in 1888[2] Although the recorded blood examinations are so incomplete as to arouse suspicion concerning their accuracy nevertheless this is an important publication because it served to direct attention to the fact that such an anemia did exist

The disease is purported to be uncommon and doubtless this is true for certainly especially in the beginnings of hematology it was recognized rarely In 1919 Smith[3] was able to collect only 64 cases A perusal of the reviews written some years ago by Root[4] and by Carey and Taylor[5] would lead one to conclude

the perianal regions and occasionally in the skin They are attributable to the diminution of the neutrophils in the circulating blood with a resultant lessened resistance to infection (3) Usually there is a pronounced and diffuse hemorrhagic tendency (4) Ordinarily the spleen is small in this condition usually weighing between 35 and 70 grams[23] but Vaughan[24] has reported that it may be enlarged (5) The characteristic findings in the bone marrow are a great increase in the proportion of fat to hematopoietic cells in some instances all of the latter may be absent with the exception of a few small groups of 2 to 3 basophil cells Occasional myelocytes and immature polymorphonuclear cells are seen The megakaryocytes are entirely absent or greatly reduced in number

It is important to note that the distribution in the bone marrow in which hematopoiesis is obviously impaired may be patchy and there may be small portions of active marrow in an otherwise distinctly hypocellular marrow In connection with these findings it should be emphasized that the blood picture does not always represent the true condition of the marrow While in idiopathic aplastic anemia it is anticipated that the marrow will always be hypocellular it is recognized that the identical blood picture may be present when the marrow is actually normal or hyperplastic in appearance In such instances the condition should be considered as atypical aplastic anemia and the cause of the anemia attributed to a diminished production of erythrocytes in the bone marrow as a result of a maturation arrest This will be considered further under the heading of atypical aplastic anemia

Symptoms and Signs

In general the symptoms may be divided into 3 main types namely (1) those usually seen in any severe anemia such as weakness and ease of fatigue pallor palpitation and dyspnea (2) hemorrhagic manifestations as indicated by bleeding from the mucous membranes and into the skin producing typical purpuric spots (3) necrotizing lesions in the mouth throat and other mucous membrane due to a decrease in the number of polymorphonuclear cells of the circulating blood

Both acute and chronic forms may be encountered In the former the condition may be of a fulminating nature in which death occurs within a few weeks to a few months The chronic type which is less common may run a course of a year or more In some instances its downward trend is interrupted by a period of remission which may persist for several months

The disease usually begins gradually with the characteristic complaints of weakness pallor dyspnea and palpitation Commonly the general nutrition is well preserved which is in keeping with the statement that the appetite is unimpaired and the weight loss in such patients is not great In the chronic form the patient may develop an amazing accommodation to the low red blood cell count

penia and the hemorrhagic tendency arising from the reduction in the number of circulating blood platelets

It should be recognized that the identical clinical picture of this disease may be observed in atypical aplastic anemia, in the secondary variety of the disease and in association with osteosclerosis

Etiology

Idiopathic aplastic anemia is a relatively rare condition which most commonly develops in females under 30 years of age

The cause of the disease is completely unknown although a number of hypotheses have been suggested The most recent intriguing suggestion is that in some instances the blood picture of aplastic anemia in man may be due to equine infectious anemia[20] By an interesting coincidence at the time this publication appeared I had under my care a girl of 16 years with aplastic anemia who was a great horsewoman The inoculation of her blood into a horse however failed to produce the disease

Whatever may be the primary cause it is clear that the fundamental mechanism underlying the anemia is the failure of the bone marrow to produce a sufficient number of erythrocytes Certainly there is no convincing evidence that increased blood destruction plays an important role in the development of the condition

It has been suggested[1] that the disease may be due to poisoning with cyclic compounds of exogenous or endogenous origin the latter arising possibly as a result of the failure of the body to detoxify certain substances Hurst[21] offered the theory that the condition might result from the absence of a hormone which regulates the activity of the bone marrow Others have advanced the idea that it may arise from a primitive and congenitally deficient bone marrow[22] At present it must be admitted that our knowledge concerning the nature of this fatal type of anemia is practically nil and that further information concerning it must be made available before any definite conclusions concerning its cause can be accepted

Pathology

The outstanding pathological changes are (1) All organs in the gross appear normal except for the anemic aspect and the frequent evidence of hemorrhage Extramedullary hematopoiesis is present to some extent and hemosiderosis may be observed (2) There are necrotizing lesions of the mucous membranes especially of the mouth and throat although they may occur also in the vagina

cells were present in the peripheral blood of all 13 patients of their group and in 3 occasional myeloblasts were also observed

The blood platelets are characteristically reduced usually below 60 000 per cubic millimeter but occasionally they have been reported as being present in normal numbers With the thrombopenia there is a prolongation of the bleeding time frequently for hours the coagulation may be normal but clot retraction is delayed

Other Laboratory Findings — The urobilin excretion the icterus index and serum bilirubin are normal although there have been reports to the effect that the icterus index is increased slightly[1] in some patients The fragility of the erythrocytes is normal Free hydrochloric acid was present in 5 of 11 cases studied by Bomford and Rhoads[1] but usually not unless alcohol or histamine was given

Prognosis and Treatment

In my experience idiopathic aplastic anemia is characterized without exception by a fatal course which occasionally is interrupted temporarily by a spontaneous remission It is reported by Vaughan however that 90 per cent of his 18 cases succumbed to the disease but it is possible that further observation may have shown that all of his cases terminated fatally The literature up to 1939 dealing with recovery in cases of idiopathic aplastic anemia has been summarized by Wintrobe Stowell and Roll[6] According to these observers recovery following aplastic anemia is exceedingly rare as indicated by the fact that they were unable to find an account of more than 0 patients who had survived more than a year after the onset of the condition and even then they could not be considered as having completely recovered

One of the most remarkable cases is the one reported by Harrison[7] This patient survived for 9 years and succumbed following a delayed transfusion reaction after having received 290 transfusions At necropsy this man was found to have a hemochromatosis

The average duration of the disease varies from a few weeks to 10 to 1 months although there have been instances in which patients have lived for much longer intervals especially when repeated blood transfusions have been given Although the outlook always is ominous it has not been in my experience as gloomy as indicated by the reports of Wintrobe Stowell and Roll[6]

Occasionally a patient with aplastic anemia may succumb to hemochromatosis It appears to be logical to assume that this may be associated with the injection of a large amount of iron intravenously in the form of the hemoglobin given in blood transfusions It is stated by Bomford and Rhoads[3] that of 3 patients with refractory anemia who developed hemachromatosis had received an

and apparently experience only symptoms which are far less than one would expect with the existing degree of anemia

On physical examination the most striking feature is an intense pallor without a lemon yellow tint in a patient in whom the loss of weight is not conspicuous In less than one half of the patients when they are first seen there is evidence of abnormal bleeding in the form of petechiae involving the mucous membranes and the skin Ulcerative lesions in the mouth may be present which vary in nature from those of a superficial character to extensive lesions resembling those seen in agranulocytosis Occasionally such lesions involve the mucous membranes of the vagina the perianal region and also the skin Slight and irregular fever is present commonly and in some instances, when there is a severe infection of the mucous membranes it may be greatly elevated and septic in type The heart rarely shows abnormal signs except a hemic murmur In my experience the spleen and lymph nodes rarely have been enlarged in the idiopathic type of aplastic anemia In occasional instances however, a slight splenomegaly has been noted but gross splenic enlargement usually casts suspicion on the correctness of the diagnosis of idiopathic aplastic anemia

Laboratory Findings

Blood — There is almost always a striking diminution in the number of red blood cells white blood cells and platelets in the circulating blood Likewise there is a comparable reduction in the amount of hemoglobin which gives a color index usually of about 1 0 Frequently the erythrocyte count is between 1 0 and 2 0 millions per cubic millimeter and the hemoglobin from 20 to 30 per cent The red blood cells appear normal in size and shape with a mean corpuscular volume usually between 90 and 100 cubic microns and a mean corpuscular hemo globin concentration of 30 to 33 per cent Hence the anemia is normochromic and normocytic in type It is not uncommon to have a reticulocyte count of between 2 and 4 per cent and occasionally there may be a few normoblasts present This is contrary to the general belief but experience has shown that such findings are not rare and that they may be accounted for by extramedullary erythropoiesis and the survival in the bone marrow of patches of normal marrow which apparently is hyperactive in releasing these erythrocyte elements

The white blood cell count commonly is below 3 000 per cubic millimeter and in some instances it has been reported to be less than 1 000 per cubic milli meter The polymorphonuclear cells invariably are reduced in number usually varying between 0 and 40 per cent Apparently it is possible to have an oc casional myelocyte present in the blood of patients with aplastic anemia as evidenced by the report of Thompson and his associates[25], who state that such

Atypical Aplastic Anemia

The term idiopathic aplastic anemia should be reserved in my opinion for a condition characterized by a hypocythemia of unknown origin in which there is a hypoplastic marrow Atypical aplastic anemia on the other hand should be employed to designate the condition characterized by the typical picture of aplastic anemia in the circulating blood associated with a normal or hyperplastic bone marrow It has been proposed by Krumbhaar[9] that the term pseudo-aplastic anemia be used for this variety with a cellular marrow

It is appreciated as pointed out by Thompson and his associates[5] that the blood changes of aplastic anemia namely a progressive decrease in the number of erythrocytes leukocytes and platelets in the circulating blood may occur in patients with variable findings in the bone marrow For this reason it becomes necessary to differentiate from true idiopathic aplastic anemia in which the marrow is hypocellular and atypical or pseudoaplastic anemia as Krumbhaar calls it in which the marrow is normal or hyperplastic In such a condition of the marrow it must be assumed that there is a maturation arrest which for some unknown reason prevents the delivery of the erythrocytes to the circulating blood at a normal rate In atypical aplastic anemia the clinical picture the spontaneous course of the disease and the prognosis are identical with that of idiopathic aplastic anemia The only differences in my experience are in the findings in the bone marrow

Secondary Aplastic Anemia

It has become clearly established that certain toxic substances may be responsible for the changes in the blood and the typical clinical manifestations which are identical with those found in the idiopathic and the atypical variety of aplastic anemia In fact the only differences between the secondary and the cryptogenic types are as follows (1) in the secondary type it can be established that the patient has been exposed to a potentially toxic substance and ( ) it is recognized that recovery may occur if the patient is removed from the possibility of further exposure to it

Most evidence regarding the relationship of an etiological factor to secondary aplastic anemia is circumstantial in nature In some instances as in the case of benzol arsphenamine irradiation and a few others the evidence although indirect is so overwhelming as to be conclusive Nevertheless it is essential when a patient is encountered with the clinical picture of aplastic anemia to direct a searching inquiry into the possible exposure to substances which might be responsible for the condition This should include questions relating to the use of drugs the nature of the diet the exposure to industrial hazards and the use of

exceptionally large number of blood transfusions and the third had been given 54 in a period of 9 years In one of my patients this complication developed following the administration of 137 transfusions given over an interval of 8 years It is estimated that during this time 68 500 c c of blood were injected, which is equivalent to 10 686 grams of hemoglobin containing 36 74 grams of iron As there is convincing evidence that in males only traces of iron are eliminated from the body in the urine and in the bile, it is likely that the iron which had been given intravenously during life accounted for the widespread deposition of metal throughout the tissues of the body It should be kept in mind that in the female the situation is somewhat different as there is normally a greater loss of iron from the body on account of pregnancy lactation and menstruation

In most instances after a variable but usually a short period of time the anemia progresses to a point where the patient's resistance is low and a terminal pneumonia results which is a common cause of death In other patients the hemorrhagic tendency dominates the picture and as a result the patient succumbs to hemorrhage into a vital organ such as the brain In a patient whom I recently observed the hemoglobin at the time of death was 95 per cent as the result of innumerable blood transfusions given over a short interval of time Death resulted however from a cerebral hemorrhage associated with a generalized uncontrollable tendency to bleed In some instances the picture of a secondary agranulocytosis may be the most important aspect of the clinical picture, and the fatal termination results from sepsis

The treatment of this condition is highly unsatisfactory In each instance a careful investigation should be made for possible toxic agents which might cause a secondary aplastic anemia because the removal of such an etiological agent, especially early in the course of the disease might result in recovery If such is found and removed no further treatment is needed

Blood transfusions are of value for two reasons, first because they supply erythrocytes and hence directly combat the anemia second because they provide blood platelets and as a result are helpful in controlling the secondary thrombocytopenic purpura They are not always successful in eliminating the hemorrhagic tendency, but all agree that blood transfusions are the most useful agent available for this purpose

No other form of therapy is of value This includes the use of intramuscular blood injections bone marrow transfusions iron liver products vitamins yellow bone marrow pentose nucleotide roentgen ray exposures to ultraviolet light splenectomy endoglobulin curettement and sulfonamide drugs None of these agents are capable of causing improvement except blood transfusions which will prolong life temporarily It does seem logical however to employ penicillin or the sulfonamides in the presence of sepsis as a result of the neutropenia which inevitably is present

anemia The associated enlargement of the spleen liver and lymph nodes results from the extramedullary hematopoiesis in these areas A comprehensive review of this condition has been presented by McCune and Bradley[40]

Osteosclerosis (Myelosclerosis)

This condition is non hereditary and usually affects adults with the findings in addition to the osteosclerosis of splenomegaly hepatomegaly lymphadenopathy and changes in the peripheral blood The spleen liver and lymph nodes show a variable degree of hematopoiesis which is responsible for their enlarge ment Cases have been described in which the peripheral blood picture resembled (1) myeloid leukemia either with or without an elevated white blood cell count (2) polycythemia (3) lymphatic leukemia and (4) aplastic anemia A complete review of the literature dealing with the various changes in the peripheral blood has been given by Jordan and Scott[41]

The only treatment which is of value in this condition is the transfusion of blood Certainly splenectomy is contraindicated

Myelophthisic Anemia

Synonyms — Myelopathic anemia osteosclerotic anemia leukoerythroblastic anemia

Definition — A slowly progressive refractory anemia due to the encroach ment of foreign cells on the normal components of the bone marrow The anemia which results is due to the decreased rate of formation f the red blood cells

Etiology

One of the most common causes for this condition is metastases from a primary cancer involving the breast prostate lungs or kidney The metastatic lesions are found most commonly in the marrow which is active in adult life Other causes are leukemia Hodgkin s disease and lymphosarcoma in which such an anemia is almost always present although it may not develop until the primary disease has become advanced Miliary tuberculosis Albers Schonberg disease (marble bones) and the primary xanthomatoses Gaucher s disease Neimann Pick disease and the Hand Schuller Christian syndrome may also be responsible for the con dition

Symptoms and Signs

The symptoms are those commonly associated with an anemia namely weak ness and ease of fatigue pallor dyspnea and palpitation in addition to the

toilet and cosmetic preparations Any substance, which includes the benzene ring, should be regarded with suspicion, as should all organic vapors with which the patient may come in contact Experience has shown that the following agents may be responsible for the production of secondary aplastic anemia

1 Benzol[9( )]
2 Irradiation[9( )]
3 Arsphenamine[31]
4 Gold[6]
5 Sulfonamides[30]
6 Dinitrophenol[3]
7 Certain hair dyes[33]
8 Trinitrotoluene[34]

In addition Bomford and Rhoads[3?] regard the following as potentially toxic substances which might be responsible for secondary aplastic anemia hydroquinone creosote resin atophan analgesic drugs as pyramidon acetanilid phenacetin and a theobromine phenobarbital compound Furthermore it is claimed that the following substances may be responsible for the syndrome mustard gas[36] bismuth[37], mercury[38] and colloidal silver[38]

Osteosclerotic Anemia

Osteosclerosis is the term employed to include those rare affections of the skeleton in which the bone marrow is encroached upon or obliterated by a proliferation of connective tissue or deposition of bone Two types of the disease are recognized namely the Albers Schonberg disease in which the so-called marble bones occur and osteosclerosis (myelosclerosis)

Albers Schonberg Disease (Osteopcrosis Marble Bone Disease)

This condition was described first by Albers Schonberg in 1904[39] It is characterized by an increase in the thickness and density of the skeletal system and by changes in the blood forming organs All of the bones of the body may be affected but the alterations are more striking in the vertebrae the pelvic bones the base of the skull the proximal ends of the femurs and the distal ends of the tibiae The bones are shown as exceedingly opaque in the roentgenograms with partial or complete obliteration of the marrow cavities The associated changes in addition to the alterations in the blood are retarded growth pathological fractures optic atrophy hydrocephalic changes chronic osteomyelitis and imperfect dentation

There is a pronounced reduction in the total amount of the bone marrow and this change logically has been regarded as the primary cause of the myelophthisic

cause the possibility that it may be myelophthisic in nature should be given serious consideration Also this type of anemia should be suspected in patients with nucleated red blood cells or immature white blood cells present in the peripheral blood with little or no anemia Of great diagnostic importance is sternal *puncture which in many instances will demonstrate the presence of foreign cells* infiltrating the marrow

Treatment and Prognosis

The treatment depends on the underlying cause of the anemia which usually is neoplastic provided one includes lymphoblastoma and leukemia in this group The outlook therefore in patients with myelophthisic anemia is not promising and the survival period is often a matter of months but in some instances it may be 5 or 6 years Not only is the outlook poor because this variety of anemia is commonly associated with malignant processes but experience has shown that when such a pathological condition has advanced so far as to produce an anemia of this type then the duration of life usually is brief

Treatment consists in the possibility of utilizing 2 therapeutic agents namely (1) the roentgen ray and (2) repeated blood transfusions If there has been bleeding and the anemia is of the hypochromic type then iron in adequate doses will be helpful The antipernicious anemia forms of therapy such as liver or stomach preparations are of no avail except in exceedingly rare instances of monocytic leukemia

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manifestations of the underlying condition which is responsible for the anemia. In some instances there is said to be deep bone pain with nocturnal exacerbations which Doan[4] considers to be pathognomonic, but this has not been a prominent feature in the cases I have seen. Almost always there is a loss of body weight with progressive cachexia. The gastric secretions usually contain free hydrochloric acid except in patients with carcinoma of the stomach. Patients with leukemia may have an elevation of the basal metabolic rate. The manifestations peculiar to the various primary causes of the anemia, such as leukemia, lymphoblastoma and others, are discussed in other chapters in Oxford Medicine.

Blood Changes

Usually when the patient is first seen, the red blood cell count is between 2.5 and 3.0 million per cubic millimeter and the hemoglobin from 50 to 60 per cent. In most instances the color index is high and the mean corpuscular hemoglobin concentration is greater than 30 per cent. The mean corpuscular volume is generally within normal limits, that is, between 85 and 95 cubic microns or slightly above normal but rarely does it exceed 110 cubic microns. In some instances the anemia may be hypochromic in nature, but this is not common in my experience. When it does occur, usually it is associated with bleeding which may result from malignancy of the gastrointestinal tract or in association with the leukemias.

The white blood cells in the circulating blood show changes depending on the nature of the disease to which the myelophthisic anemia is secondary. In leukemia, lymphosarcoma and sometimes multiple myeloma, abnormal white blood cells may be present. The platelet count may be normal or reduced. The latter state usually is pronounced in the acute leukemias and is associated frequently with a tendency to bleed abnormally.

In some patients the most significant feature of the blood is the presence of large numbers of immature red blood cells which is out of proportion to the degree of the anemia. In one patient with myelogenous leukemia whom I observed, although the anemia was not severe and the white blood cell count was normal, the number of normoblasts was so great that the diagnosis of chronic hemolytic jaundice was strongly considered.

Diagnosis

Usually the diagnosis of a myelophthisic anemia is obvious on account of the presence of unmistakable signs of such conditions as leukemia or lymphoblastoma which are commonly responsible for it. In some instances, however, the underlying nature of the anemia may not be suspected. Hence when a normochromic normocytic or slightly macrocytic anemia is observed in a patient without obvious

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MEDITERRANEAN ANEMIA

Synonyms — Cooley's anemia, Erythroblastic anemia Thalassemia

Definition — Mediterranean anemia is a rare chronic, often progressive microcytic hypochromic anemia of obscure etiology occurring with equal frequency in the two sexes It develops almost always in infancy and childhood and is characterized by a racial, congenital and often a family incidence, erythroblastosis decreased fragility of the erythrocytes splenomegaly, hyperplastic changes in the bone marrow typical roentgenological changes in the bones, mongoloid facies and a refractoriness to iron therapy

History

Patients with this type of anemia were described originally by the late Thomas B Cooley the well known pediatrician of Detroit, Michigan In 1925 he with Dr Pearl Lee[1] presented the abstracts of 5 cases before the meeting of the American Pediatrics Society At this time he stated that such cases had been regarded previously as von Jacksch's disease or pseudoleukemia The anemia splenomegaly the discoloration of the skin the absence of bile from the urine and the many nucleated red blood cells in the circulating blood were described accurately The mongoloid features and the roentgen ray alterations were noted also In a later publication he gave a more complete description and ventured the opinion that, although the hemolysis is a constant feature the condition should not be considered as primarily a hemolytic disorder

Excellent summaries of our knowledge of the disease have been written by Baty Blackfan, and Diamond , Parsons and Hawksley[3], Yaguda[4] and Flynn[5] In 1936 Whipple and Bradford[6] made a comprehensive pathological study of the condition and tested many therapeutic agents without avail They considered that the condition might be due to some racial inherited defect or possibly a deficiency state The name 'thalassemia' derived from the Greek meaning 'great sea' was suggested by them to replace the original designation of 'erythroblastic anemia' by Cooley

Etiology

Age and Sex

The earliest manifestations of the condition may appear at any time during the initial decade of life but usually they are noted during the first 2 years the

average being about 16 months The symptoms at the onset ordinarily are of such slight intensity that medical attention is not sought until the age of 3 years or older It is becoming increasingly apparent that the disease may be so mild that it is not recognized until adult life or the symptoms may be so insignificant that the condition is entirely overlooked unless it is discovered by a routine blood examination The disorder described as target cell anemia by Dameshek[7] and a condition resembling Mediterranean anemia in Italian adolescents and adults observed by Wintrobe and his collaborators[8] are probably the same or closely allied diseases but atypical and of a less disabling nature which permits persons to attain adult life

The disease occurs with equal frequency in both sexes

Hereditary and Racial Incidence

It is certain that the malady occurs with greatest frequency in persons of the Mediterranean countries namely Greeks Italians and Sicilians This racial distribution has been accepted in general but cases have been noted in other races than those named and in my experience it is becoming more common to observe the condition in persons of non Mediterranean origin Cooley committed himself to the belief that there is not a strict racial distribution for he was of the opinion that there is no such thing [9] He stated that when a disease producing mutation takes place there is evidence that it will first occur in the neighborhood of its origin Furthermore it will be limited to a community a province or a race in proportion to the clannishness and isolation of the people involved Regardless of whether or not these statements are correct it must be conceded that in a great proportion of the reported cases the racial incidence has been impressive Recently it has been my experience to encounter an increasing number of individuals with the condition who have not had their origin in the countries of the Mediterranean area It is possible therefore that the prediction made by Cooley is now becoming apparent

It was Cooley s opinion that sufficient data had been accumulated to say that the condition was hereditary and suggestive evidence indicates that it might be transmitted as a simple dominant characteristic The fact that some cases may be mild and hence overlooked makes difficult an accurate study of the hereditary features

A most comprehensive consideration has been given to the possible genetic aspects of the disease by Valentine and Neel[10] These investigators studied four families including 34 persons in whom the disease was prevalent They made an observation of the utmost importance namely that in every case in which a complete hematological examination was carried out of both parents of a patient having this type of anemia it showed that each one was afflicted with

the disease The one exception to this statement is the case reported by Smith[11] These observers finally conclude, after considering all of the facts relative to the hereditary transmission of the disease that ' for the present it seems best to view the hypothesis of an incomplete recessive character as the most satisfactory working approach to the problem, depending on the collection of further data'

Nature of the Disease

Although there is a very definite element of hemolysis in the production of the anemia, it is generally agreed that this is not the fundamental cause Deposits of iron staining granules throughout the body suggest a disturbance of pigment metabolism but the real factors responsible for the disorder are obscure Cooley s belief was that the disease is concerned primarily with some disturbance of metabolic function with a secondary effect on the bone marrow and reticulo endothelium The statement, however, is a vague and general one which neces sarily lacks desirable conclusiveness It does seem clear that in the early stages of the malady most of the changes in the red blood cells are lacking

It is the belief of Whipple and Bradford[6] that the cause is concerned with an inherited defect which involves the hematopoietic and osseous system They suggest that it may be a deficiency of a vitamin or endocrine nature acting in a manner similar to the deficiencies of pernicious anemia or scurvy They also call attention to the fact that the peculiar pigment distribution is seen in only one other condition namely hemachromatosis It is considered by Valentine and Neel[10] that the basic defect which is the fundamental cause of the disease is an inherited inability to utilize or synthesize some substance necessary to normal blood formation If this hypothesis is correct, it must be admitted that it has not been possible to identify the missing elements in this type of anemia In Wintrobe s opinion[1] the appearance of the red corpuscles and their increased resistance to saline hemolysis suggests that the inherited defect is one in which the corpuscles are formed with an adequate or excessive cell membrane but with little substance They could be pictured as a half inflated basketball bladder As a result the cells are able to absorb more fluid than normal cells without bursting The other characteristics he believes can be explained by the assump tion that they are compensatory in nature for faulty red blood cell formation

In some respects Mediterranean anemia appears to be related to sickle cell anemia and congenital hemolytic icterus as it is definitely familial and appears to be due to an inherited defect

Pathology

At necropsy there is a generalized edema and fatty changes in the heart liver and kidneys Deposits of an iron-containing pigment simulating the findings in

hemachromatosis are present in the liver pancreas lymph nodes gastric mucosa endocrine glands and elsewhere in the body The heart often is hypertrophied which is attributable to the long standing anemia The liver and spleen are grossly enlarged The bones show two types of changes namely an atrophy of the trabeculae and shafts of various bones and a delicate proliferation of new bone in association with thickening of the calvarium which produces the typical changes in the roentgen ray The ribs may show the same type of thickening The bone marrow characteristically is hyperplastic as in pernicious anemia and primitive stem cells are abundant Nucleated red blood cells myelocytes and megakaryocytes are numerous Phagocytes are present and may contain iron pigment Foam cells are observed in small islands and there may be areas of fibrosis

Symptoms and Signs

Usually the onset which most commonly occurs in infancy or childhood is insidious and dates from the time the parents first note the present of pallor Often this is associated with a yellowish tint but usually it is without sufficient intensity to be called jaundice Almost always the spleen becomes enlarged early in the course of the disease With the progressive pallor associated with an intensification of the anemia there is a protuberance of the abdomen and increasing weakness ease of fatigue dyspnea and palpitation It is not uncommon to have unexplained episodes of fever for which no cause can be found Other complaints may be anorexia occasional vomiting pain in the upper abdomen and an enlargement of the head Pathological fractures are rare but they have been known to occur

Physical examination may show no evidence of undernutrition but commonly growth and normal development are retarded after the first year Mentally the patients are normal As emphasized by Baty and his associates[2] the general appearance of these patients is so striking that a presumptive diagnosis can be made by inspection alone They bear a closer resemblance to each other than they do to normal members of their own family Usually there is a distinct pallor with a sallow but not a definite icteric tint This has been described as a muddy color and possibly results from a combination of racial color of the skin and pallor although iron deposits in the epidermis may be of some importance in this connection

On inspection certain signs at once attract attention (1) the features are mongoloid as indicated by prominent eyes sometimes an epicanthal fold high malar bones a short nose with a depressed bridge and the peculiar muddy pallor (2) the head is large and irregularly shaped with prominent frontal and parietal bases in long standing cases there may be a sulcus like depression in the upper

surface of the skull along the superior saggital suture line due to a widening of the diploe on either side, (3) the stature is small, and the general body development is retarded (4) there is commonly a striking prominence to the abdomen

The enlargement of the abdomen often is asymmetrical for the increase in size is greater in the upper regions and especially on the left side due to the splenomegaly The latter is present to a variable degree depending on the stage of the disease, as it tends to become more prominent as the condition progresses The spleen may reach only slightly below the costal margin in early cases but projects to the brim of the pelvis or lower in the advanced stages The liver also is increased in size but not to the same extent as the spleen It is usually two or three finger breadths below the right costal margin The veins of the anterior abdominal wall frequently are dilated and there may be an umbilical hernia resulting from increased intra abdominal pressure

The peripheral lymph nodes frequently are enlarged and may be observed as non tender small discrete nodes, usually in the inguinal and cervical regions but also they may be found elsewhere When the patients are first observed, there is almost always enlargement of the heart and a hemic murmur

Roentgenological Findings

As the bone marrow in this condition is hyperplastic and over active it is to be anticipated that changes would occur in the skeleton system which are demonstrable in roentgenograms In the cranium there is a characteristic thickening of the vault as a result of widening of the diploic spaces while the tables usually are thin In the early cases of the disease the skull may show only slight thickening with diffuse osteoporosis When the condition is well established, there is a wider diploic space 2 to 2 5 millimeters with a striking appearance caused by the vertical striations at right angles to the inner tables, this is the so called 'hair on end' appearance The outer table may be absent The non striated portion of the skull sometimes has a spongy appearance due to osteoporosis Uniform widening of the medullary canals of the long and short bones is present and the cortices are thinned and spread apart The bones are generally osteoporetic Heavy trabeculations especially near the ends of the shafts are seen often to cross irregularly through the medullary spaces The flat bones may be osteoporetic also but with increased reticulation and a fan like radiation

The importance of the early bone changes is emphasized by Caffey[13] who believes that the first alteration to occur in the skull is a thickening of the lower frontal squamosa Radial striations develop first in the anterior portion of the parietal bones near the sagittal suture He states that the frontal bone is the site of the initial and most pronounced thickening The initial lesions of the

long bones he regards as dilatation of the medullary canals with simultaneous atrophy of cortical and cancellous bone In 2 mild cases which he observed with the onset late in life, there were no skeletal changes

Changes in the Blood

The blood shows no distinctive changes in the early stages of the disease The large number of normoblasts which are so characteristic, appear later When the condition is fully developed the red blood cell count averages between 2 and 3 millions per cubic millimeter and the hemoglobin between 20 and 40 per cent The anemia is characteristically of the microcytic hypochromic type A young Greek boy 14 years of age whom recently I have had under my observation had a red blood cell count of 1 9 million per cubic millimeter with a hemoglobin of 14 per cent 2 grams per 100 c c of blood The mean corpuscular volume in this patient was the lowest I have ever seen being 47 cubic microns This was on account of the excessive fragmentation of the erythrocytes and hence the presence of many exceedingly small red cells in the circulating blood

When the condition is fully developed in addition to the erythroblastosis there is polychromatophilia extreme poikilocytosis and anisocytosis The reticulocytes usually are increased to 5 or 10 per cent Of great importance from the stand point of diagnosis is the presence of macrocytes which are observed usually and in some instances assume a huge size Three varieties of these cells are seen One type has been designated as a target cell on account of the deeply stained center and a periphery which may be arranged in concentric alternating light and dark zones The second type is a round or sometimes a slightly oval cell with an extremely narrow rim of cytoplasm and a large central area of achromia The third and the most characteristic macrocyte of the disease is a large pale red cell which contains irregularly distributed hemoglobin arranged in clumps and whose intervening areas stain imperfectly All 3 types of macrocytes are extremely thin

The presence of nucleated red blood cells is the characteristic finding from which the disease derives one of its names erythroblastic anemia These are typical fully developed and early normoblasts and micronormoblasts There may be 2 or 3 times as many nucleated red blood cells as there are white blood cells

The leukocytes are increased in number usually varying between 10 000 and 25 000 per cubic millimeter although counts as high as 100 000 per cubic millimeter have been recorded There may be myelocytes and occasionally myeloblasts present but they are observed usually only in small numbers

There are no significant changes in the blood platelets

In most instances there is increased resistance of the red blood cells to hypo

tonic salt solutions It has been reported that occasionally hemolysis is not complete in 0 2 per cent salt solution or even in distilled water

The icterus index often is elevated usually being between 8 and 30 units and there is a corresponding increase in the blood bilirubin The urine may show a urobilinogen content above normal which has been interpreted as evidence of abnormal hemolysis

Red Blood Cell Volume Hemoglobin Content Erythrocyte Thickness

Studies by Bradford and Dye[14] have demonstrated that undoubtedly these patients have a microcytic hypochromic anemia as shown by volume measurements despite the possibility that the extreme fragmentation might introduce errors into the calculations They found that the mean corpuscular volume usually was less than 77 cubic microns and that the mean corpuscular hemoglobin concentration was less than 30 per cent Cell thickness, calculated by the three dimension chart of von Boros did not show that the cells averaged much less than normal in thickness They regard normal thickness when measured by this method as 2 1 microns and in patients, in whom the average cell thickness was determined the measurements were as follows 2 1, 2 3, 1 35, 2 05, 2 07 and 2 0 microns[14]

Mediterranean Anemia in Adolescents and Adults

When this disorder was first described it was considered to be limited to children, usually under 14 years of age because it was thought that few, if any, survived to adolescent or adult life This is now known to be incorrect, because it has been observed in older children and even in adults and also because it is now recognized that it may exist in an exceedingly mild form which is not detected unless a blood examination is done In other words an individual with the latter type of the disease could be regarded as being in a carrier state Cases of mild or atypical anemia which undoubtedly is a variety of Mediterranean anemia, have been reported under the title a familial disorder in Italian adolescents '[8] and target cell anemia [7] These patients most frequently have been of Italian origin but more recently cases have been reported in Greeks and also in a child from Porto Rico of Scotch and Spanish origin

Such adult patients may have few if any symptoms although some degree of anemia may be present and splenomegaly is not uncommon The red blood cell count may be slightly below normal The hematocrit usually is reduced which means that with a normal or increased red blood cell count the erythrocytes must have a mean corpuscular volume which is less than normal Also the hemoglobin level is commonly below normal limits With a microcytosis and

hypochromia it would be anticipated that iron therapy might be beneficial but this is not the case This is the only type of hypochromic anemia which is not amenable to iron therapy, as far as I know

In addition these patients show undue changes in the circulating erythrocytes considering that the red blood cell count and hemoglobin deviate so slightly from normal in many instances There may be hypochromia poikilocytosis target cell shapes stippling in some instances and increased resistance to hypotonic saline solutions It appears justifiable to regard these cases as mild forms of erythroblastic anemia in persons who have survived to adult life At this age as they are capable of reproduction the trait may be transmitted to their offspring

The existence of the carrier state has been suggested by Valentine and Neel[10] They propose the names thalassemia major and thalassemia minor the former being the fully developed disease and the latter the carrier state The chief difference between the two in their opinion is a quantitative one namely in thalassemia major there are circulating erythroblasts which frequently occur in numbers out of proportion to the degree of the anemia

Other diagnostic criteria which may be applied to the adult type of Mediterranean anemia have been enumerated by Dameshek[7] as follows the presence of a racial factor a hypochromic condition of the blood which is refractory to iron therapy the presence of target cells oval and stippled cells in the circulating blood the increased resistance of the erythrocytes to hypotonic solutions of sodium chloride and the absence of other conditions in which target cells are found It has been suggested that the carrier state may mimic other conditions such as rheumatic fever lead poisoning hemolytic jaundice and the various splenomegalies A remarkable family of Italian descent was observed by Coldhamer[15] in which there were 8 cases in 3 generations with either highly characteristic or suggestive changes in the blood of Mediterranean anemia He considered that these individuals represented forms of the adult type of Mediterranean anemia which varied in severity but in all instances was less severe than true erythroblastic anemia as seen in children

Secondary Erythroblastic Anemia

The term secondary erythroblastic anemia is employed by Higley[16] to indicate that a blood condition characterized by the presence of many nucleated red blood cells may occur secondary to some recognizable disease Some of the conditions which have been reported as producing or accompanying an erythroblastic blood picture are as follows

1 Excessive exposure to roentgen ray or radioactive material
2 Chemical or drug poisoning

3 Malignancy with metastases to the bone marrow
4 Chronic diarrhea as found in rickets scurvy or steatorrhea
5 Recurrent and severe hemorrhage
6 Chronic or severe infections
7 Malformations of the circulatory system such as congenital heart disease or arteriovenous aneurysm
8 Hemolytic anemias
9 Extramedullary hematopoiesis associated with enlargement of the liver and the spleen
10 Myelogenous leukemia
11 Multiple myeloma
12 Myelosclerosis and myelofibrosis of obscure etiology
13 Marble bone disease of Albers Schonberg
14 Polycythemia
15 Agnogenic myeloid hyperplasis of the spleen

Treatment

The treatment of Cooley s or Mediterranean anemia is extremely unsatisfactory as it is purely symptomatic Nothing has been discovered to date which influences the condition favorably It is one type of microcytic hypochromic anemia which is completely resistant to iron therapy as this metal alone in large doses or in combination with copper pyridoxin liver or any other material produces no beneficial effect

Splenectomy is claimed by some to be helpful but the most that can be said is that it produces a slight and transient improvement in the blood picture and relieves the child of the weight of the spleen which is often considerable

Roentgen ray therapy has been tried without demonstrable effect but this form of treatment has not had a sufficient trial and should be employed in more cases before a final conclusion is reached in regard to its value

Blood transfusions are useful in fact they are the only therapeutic measure which is known to accomplish good but the improvement they produce is only transient

A number of substances claimed to have been of value in this disease were given a trial by Whipple and Bradford[5] who made the following statement concerning their effectiveness The following therapeutic measures which we believe have been adequately tested failed to modify the clinical picture blood transfusion plasma and cell extracts primary and secondary liver extracts fetal liver extract spleen extract raw pancreas adrenal cortex extract (cortin) estrogenic substances (progon) vitamin B_1 concentrate iron and copper

Prognosis and Course of the Disease

Once this disease is established it usually progresses with an almost imperceptible increase of symptoms from day to day without remissions until a fatal issue occurs If the onset is at an early age the period of time is less before the patient succumbs In general it can be said that the malady usually begins in infancy often continues throughout childhood but rarely is there survival until adult life It is now thought however that more attain adult life than previously had been supposed This is because the carrier state is known to exist These are mild cases with few if any symptoms and hence the disease would be unrecognized unless the blood were examined

In the average patient the onset is in infancy the symptoms gradually progress over a period of months or years and eventually the patient succumbs to an intercurrent infection to which he is known to be peculiarly susceptible or to a cardiac complication

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ERYTHROBLASTOSIS FETALIS

Synonyms —Erythroblastosis neonatorum hydrops fetalis icterus gravis congenital anemia of the newborn erythroleukoblastosis fetal anemia

Definition —The syndromes of hydrops fetalis icterus gravis and congenital anemia of the newborn although presenting different clinical pictures are all included under the general term of erythroblastosis fetalis This is because the three conditions have the following characteristics in common a severe anemia extensive extramedullary hemopoiesis erythroblasto is hepatomegaly splenomegaly and the fact that successive members of the same family may show evidences of any of the three clinical types of the disease

History

As the term erythroblastosis fetali is employed to describe three somewhat dissimilar clinical conditions all of which have the same blood picture of excessive hemolysis and abnormal hemopoiesis the historical aspect of the subject must necessarily be concerned with tracing the development of our knowledge concerning each of the three entities They have been known in the past as fetal hydrops familial icterus gravis and certain cases of congenital anemia

The best known early monograph dealing with universal edema of the fetus is that of Ballantyne[1] who in 1898 collected 70 cases the first having been recorded in 1614 To Schridde in 1910 must go the credit for the initial description of certain types of universal edema in infants associated with the causative disturbance in the hemopoietic organs Rautmann[3] in 1912 applied the name erythroblastosis to the underlying hematological condition

Early cases of icterus gravis neonatorum were reported by Blomfield[4] in 1901 Arkwright[5] in 1902 and others but they mentioned only the familial incidence the intensity of the icterus and the ominous outlook and failed to recognize the underlying pathology of the disease The erythroblastosis was first recognized as a part of the clinical picture by Buchan and Comrie in 1909[6]

The presence of an unusual type of anemia in newborn infants was reported by Finklestein in 1911[7] and by others In 1909 Buchan and Comrie[6] observed the presence of a severe anemia in 4 of the infants they studied at birth Priority for the recognition of the anemia alone however usually is accorded to Ecklin[8] who in 1919 described a severe case of anemia in the newborn

In 1932 Diamond Blackfan and Baty[9] gave an excellent review of the literature dealing with this subject and reported the details concerning o cases They concluded that the universal edema of infants familial icterus neonatorum and

anemia of the newborn were closely related conditions which were dependent upon the same underlying pathological process The recent outstanding discovery that erythroblastosis fetalis is due to a reaction to the Rh factor is discussed in the following section on Etiology

ETIOLOGY

The first intimation that iso-immunization of the mother by dominant hereditary blood factors in the fetus might account for the hemolysis of the fetal red cells in this disease was in 1939 At this time Levine and Stetson[10] reported a transfusion reaction in a pregnant woman, in which it was assumed that the reaction could be attributed to an agglutinin resulting from immunization of the mother by factors in the fetus inherited from the father In 1941 Levine Katzin and Burnham[11] reported 5 additional patients with atypical agglutinins 3 of whom gave birth to infants suffering from erythroblastosis It was their opinion at that time that the evidence indicated that most of the serums contained an agglutinin which paralleled the anti Rh agglutinin of Landsteiner and Wiener[12] first reported in 1940 It is the opinion of Levine and his associates that atypical iso-agglutinins are produced in the mother in response to certain antigenic factors (the Rh factor) which are present in fetal blood but not in the blood of the mother (Rh negative blood) The maternal atypical agglutinins serve to initiate the intra uterine hemolysis in the blood of the fetus which is the characteristic feature of erythroblastosis fetalis Since the Rh factor is limited to the red blood cells it must be assumed that fetal erythrocytes pass into the maternal circulation to stimulate the iso-immunization of the mother The mechanism of this is not clear at present Once anti bodies are produced in the mother no difficulty is experienced in understanding their passage through the placenta as such a mechanism provides for the immunological defense of the newborn against some of the infectious diseases

In the concluding paragraphs of Levine s most excellent and extensive review of the subject of erythroblastosis fetalis he[13] states The remarkably varying clinical manifestations of erythroblastosis fetalis are entirely compatible with the iso-immunization theory One may assume that the fetal hydrops is the end result of intense iso immunization over a prolonged period while anemia of the newborn infant is the condition to be expected from a shorter duration of the same process By the same token the two extreme forms should be rare in contrast to the more frequent intermediate variety icterus gravis Now that the source of the intra uterine hemolysis is established there is no conflict whatever between the striking variations in clinical manifestations and the one uniform characteristic pathologic feature of blood destruction and extramedullary hemopoiesis

The importance of this condition may be judged from the figures of Javert[14] who found that the incidence of erythroblastosis in his experience was one case to every 438 births with a fetal mortality of 3 per cent

It should be kept in mind that erythroblastosis as evidenced by a large number of nucleated red blood cells in the circulating blood may develop in infants who do not have hemolytic anemia resulting from Rh incompatibility This condition according to Diamond[15] may arise also in the presence of infection with congenital malformations of the heart with anoxemia due to atelectasis of the lungs with intracranial hemorrhage and even in extremely premature infants Such conditions may be differentiated from hemolysis due to Rh incompatibility by the demonstration of an Rh negative mother an Rh positive infant and anti Rh agglutinins in the mother s serum When the conditions just stated are present then the erythroblastosis is known to be due to Rh incompatibility

Pathology

At necropsy infants with this condition reveal characteristically a deep yellow staining of all internal viscera the skin serous membranes sclerae and fat tissues Other gross changes are the enlargement of the liver and spleen the pallor which is apparent despite the presence of jaundice and small ecchymotic hemorrhages in the skin and serous and mucous membranes There is some disturbance of pigment metabolism as indicated by the presence of large amounts of hemosiderin in the hepatic cells the Kupffer cells of the liver the endothelial phagocytes of the spleen and the epithelial cells of the convoluted tubules of the kidneys

The bone marrow shows active hemopoiesis often in excess of normal and in some cases there may be overcrowding of the marrow spaces [illegible] often striking extramedullary blood formation as indicated by foci of hem[illegible] in the enlarged liver and spleen the kidneys adrenals pancreas, lymph [illegible] thyroid gland gonads and other organs

Symptoms and Signs

The classification of cases of erythroblastosis fetalis based [illegible] ing manifestation in a study of 47 cases suggested by Ja[illegible]

Erythroblastosis with hydrops	[illegible]
Erythroblastosis with icterus	[illegible]
Erythroblastosis with anemia	[illegible]
Erythroblastosis with hemorrhagic diathesis	[illegible]
Unclassified (without hydrops icterus or anem[illegible]	[illegible]

of nucleated red blood cells are present in the circulating blood A leukocytosis varying from 25 000 to 50 000 per cubic millimeter is observed often and a few myelocytes or occasional myeloblasts may be present Blood films reveal the presence of megaloblasts with large nuclei containing a loose chromatin network several nucleoli and a basophilic cytoplasm Mitotic figures are observed frequently *Normoblasts frequently are present in large numbers In the patients* who survive there is a gradual decrease in the number of nucleated red blood cells so that at the end of a week or 10 days there is usually a complete disappearance of them from the circulating blood

Treatment

The outlook for patients with this condition is ominous for if the infant is not dead at birth a fatal issue is likely to occur within 6 to 12 days In addition to supportive measures such as oxygen inhalations and artificial feedings blood transfusions are indicated

It is suggested by Wiener and Wexler[16] that as soon as the diagnosis is made or even suspected arrangements should be made for transfusion with Rh negative blood since the condition clearly constitutes a medical emergency They state *that no time should be lost in waiting for the laboratory findings such as the Rh* test firstly because there are atypical cases in which the subtypes of the Rh factor are involved and secondly because of the possibilities of technical errors in determining the Rh type particularly in an emergency test The blood always should be given intravenously usually by a scalp vein but if this is not possible then a vein should be made accessible by incision in the region of the antecubical fossa or the internal malleolus

These authors remind the physician that in cases where the mother has given a history of previous still births or infants born with erythroblastosis the appearance of the disease can be anticipated before the infant is born In such instances it is suggested that a prophylactic tran fusion be given in the umbilical vein before it is tied and cut It is recognized that Rh negative blood is most suitable and theoretically *the donor should be of the same group as the infant* In practice however group O serves as well because of the relative insensitivity of the infant s cells to the alpha and beta agglutinins

It is rational to employ only Rh negative blood in these infants because many of them still have anti Rh agglutinins in the circulating blood which have not combined *with their own positive cells These agglutinins are therefore* potentially active in hemolyzing any Rh positive cells which may be introduced into the circulation by transfusion Rh negative blood cells cannot be affected by such *abnormal agglutinins* and it is known *that they survive in the infant s* circulation It is probably not wise to permit the infant to use the mother s

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breast milk This is because it has been shown[17] that anti Rh agglutinins may be present in the milk and after absorption from the gastrointestinal tract they might produce further hemolysis of the infant s red blood cells

It is pointed out by Wiener and Wexler[16] that to control hemorrhagic symptoms transfusions of fresh whole blood or plasma containing platelets and fibrinogen might be effective whereas washed erythrocytes or stored blood or plasma would not be Some infants might receive maximum benefit from the use of mother s washed red blood cells suspended in plasma of a donor of a compatible group

According to Diamond[15] there are two methods of proven value which may be employed in assisting a previously sensitized mother to have a living Rh positive infant One takes advantage of the knowledge that the anti Rh titre in the blood of women who have previously had an infant with erythroblastosis fetalis tends to increase relatively late in pregnancy, usually not until the 7th or 8th month It has been reported[15] that in 41 cases of early induction of delivery on account of a rising titre of anti Rh agglutinin there have been 32 living and 9 dead children It is possible, therefore to induce labor when these circumstances prevail in a pregnant woman at $8\frac{1}{2}$ months and secure a viable infant The other method is artificial insemination using an Rh negative donor This has been reported by Diamond[15] and by Potter and Willson[19] Needless to say the emotional factors associated with the latter procedure make it unlikely that it will be employed on a large scale

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BLOOD TRANSFUSION

Introduction

The technic of the injection of human blood obtained from one person into the veins of another has now become so perfected that it is regarded as a common place and exceedingly useful therapeutic procedure Since 1914 it has been demonstrated that the citrated form of blood transfusion is more practical and just as effective as when unmodified blood is employed Furthermore, in more recent years experience has shown the great value of the blood bank, especially in large institutions Substantial progress has been made since the onset of the World War II as a result of intensive investigations regarding the value of various types of substitutes for blood which have been introduced into military and clinical medicine

History

The history of the development of our knowledge of blood transfusions is fascinating from many standpoints as it involves almost every phase of medicine and is fraught with national and personal controversies relating to claims of priority and jealousies which arise so often in many fields of human endeavor For convenience the history of the development of our knowledge of this subject *may be divided into four periods as follows*

First Period —This dates from the very earliest times of the ancient Greek and Egyptian civilization to 1616 when William Harvey discovered the circulation of the blood There were no important contributions to the subject in this long interval The often repeated story of the administration of blood transfusions to Pope Innocent VIII cannot be substantiated and it is probable that the ailing Pontiff drank the blood rather than having it injected into his veins The only other incident of the early period which is of interest, is the remarkable *statement of Libavius the Chemist of Halle* made in 1615 *in which he describes* what is now considered to be a fictitious blood transfusion

Second Period —This brief interval lasting from 1656 to 1670 was a fruitful one It was during this time (1656) that Sir Christopher Wren the versatile architect astronomer and scientist first gave an intravenous injection which led to the initial transfusion of blood from one dog to another in 1665 by Richard Lower Professor of Physiology at Oxford England Other workers at this time including Johann Sigismund Elsholtz gave intravenous injections which were described in his book Clysmatica Nova" published in 1665 Although

Lower did give a transfusion of lamb s blood to man it is known that he was preceded in this by that remarkable Frenchman Jean Baptiste Denys of Mont pellier who recorded his experiments in the Transactions of the Philosophical Society for July 22 1667, which antedated a similar transfusion of Lower by several months As a result of the inevitable serious untoward effects following the trans fusion of lamb s blood the procedure very properly fell into disrepute and no further progress was made for an interval of the next 150 years

Third Period — This is inaugurated by the epoch making experiments of James Blundell physiologist and obstetrician who was the first to perform a transfusion of human blood into another human being which was accomplished in London on September 26 1818 Although a number of transfusions were given by Blundell they were not uniformly successful because the procedure could only be tried on patients who were in extremis there was no way in which the blood could be kept from clotting and of course at that time there was no knowl edge of the blood groups so that unfavorable reactions could be averted

Fourth Period — The fourth era the modern period dates from the time the blood groups were identified by Landsteiner in 1901 and includes the interval in which sodium citrate was introduced to prevent clotting in 1914 It was on March 27 1914 that Albert Hustin collected 150 c c of blood from a donor re ceived it in a mixture of glucose and sodium citrate and injected it into the veins of a patient who had an anemia due to intestinal hemorrhage This information I have from a photostat copy of Hustin s diary which he was so kind as to send to me The data was published the following April in the Bulletin des Sciences Medicales et Naturelles de Bruxelles

It is an amazing fact that in a short period of 9 months in 1914 and 1915 three additional separate investigators reported independently on the citrate method of blood transfusion for which the world had been in such dire need for so many years Those to whom credit should be accorded in this respect are Louise Agote[1] Richard Lewisohn[2] and Richard Weil[3]

With the control of the clotting process in blood transfusions and the recogni tion of the blood groups by Karl Landsteiner which has been previously men tioned the technic of the procedure became satisfactorily standardized Although Landsteiner s contribution had been made in 1901 it was not until 1908 that Ruben Ottenberg[4] published his studies which indicated the importance of selecting donors rigidly on the basis of agglutination tests

The first observation which led to an appreciation of the importance of the Rh factor as a cause for intravascular hemolysis of the donor s erythrocytes by the recipient s serum was made by Levine and Stetson in 1939[4( )] These observers reported a transfusion reaction in a pregnant woman which they attributed to an agglutinin resulting from immunization of the mother by factors in the fetus inherited from the father

In 1940 the Rh blood types were recognized by Landsteiner and Wiener[5], and in the same year it was emphasized by Wiener and Peters[6] that the indiscriminate use of Rh positive blood could be responsible for a serious or even fatal hemolytic reaction following a blood transfusion in a recipient who was Rh negative

Other important advances in this field have been the introduction of the blood bank in warfare by Oswald Robertson in 1918[7], the studies on cadaver blood by the Russians Shamov[8] and Yudin[9] which stimulated the formation of the first blood bank in a large hospital in this country at the Cook County Hospital in Chicago in 1937 and the introduction of desiccated blood plasma as a blood substitute which followed the work of Elser[10], Flosdorf and Mudd[11]. The remarkable advances by Edwin Cohn and his associates in separating the various fractions of plasma are summarized in the July, 1944 issue of the Journal of Clinical Investigation

Indications for Blood Transfusions

There are a number of indications for blood transfusions which are based on the physiological and pathological changes of blood the main ones being as follows

1 To increase the hemoglobin content of the blood in patients with anemia and thereby combat anoxemia

2 To increase the blood volume in order to maintain the efficiency of the circulatory system

3 To augment the protein content of the blood and sustain the proper osmotic pressure relations with the body tissues

4 To correct coagulation defects by making available functionally effective prothrombin, thromboplastin platelets and fibrinogen

5 By the addition of immunological fractions to combat infection

From a practical standpoint basing the indications on the above statements, blood transfusions should be useful in clinical medicine under the following circumstances (1) in treating anemias when no other form of treatment is available (2) in order to sustain a patient with anemia until a diagnosis can be made or until potent antianemic therapy becomes effective (3) as a preoperative or postoperative measure in patients with anemia (4) in the treatment of acute or chronic hemorrhage (5) as a therapeutic measure in shock (6) as a means of expediting the return of the blood to normal in patients with chronic hemorrhage when the source of the bleeding has been controlled (7) as an adjunct to other forms of combating infection (8) in the treatment of hypoprotenemia and (9) as a means of controlling the bleeding in thrombopenic purpura hemophilia and hypoprothrombinemia

Treatment of Anemia When No Other Forms of Therapy Are Available

All too often one is confronted with a patient who has an anemia for which there is no specific therapy In some instances the primary condition can be relieved by surgery, or an infection may be controlled but often nothing further can be done except to administer repeated blood transfusions which are of considerable value and should be given Such anemias are aplastic anemia myelophthisic anemia the anemia of nephritis the anemia of malignancy lymphoblastoma leukemia Cooley s anemia sickle cell anemia and achrestic anemia

I am a strong advocate of employing all measures in the treatment of anemia in malignancy regardless of the cause This is on the basis that the patient often is made more comfortable due to the relief of extreme weakness and ease of fatigue If pain is present it can be controlled readily by liberal use of morphine In some patients if the anemia is due to chronic hemorrhage it can be benefited materially by the administration of iron or providing a better diet Occasionally liver is of benefit If none of these measures are helpful then repeated blood transfusions should be given until the maximum improvement is derived

Use of Blood Transfusions to Sustain the Patient Until a Diagnosis Can Be Made or Until Potent Antianemic Therapy Can Become Effective or as an Essential Preoperative and Postoperative Procedure

Patients with a remedial anemia when observed for the first time are in some instances in such a precarious shape that they may expire before a specific form of therapy has sufficient time to exert its beneficial effect I have seen this happen in the early days of the liver treatment of pernicious anemia If in the case of patients with pernicious anemia the red blood cell count is 1 0 per cubic millimeter or less it is frequently our practice at the Simpson Memorial Institute to give one or more blood transfusions as a safeguard in order to bridge over the 24 to 48 hours between the time when the treatment is given and when it becomes effective

Blood transfusions undoubtedly may be a life saving measure in the preoperative and postoperative treatment of patients with an anemia It has been clearly established that one or more can convert a poor operative risk into a good one Their value has been established so adequately that major surgery should not be attempted without having adequate facilities for administering blood transfusions in any number promptly and safely to surgical patients in whom the indications arise It is my opinion that unless a major operative procedure is urgent it should be deferred if an anemia is present until the hemoglobin is at least 80 per cent (12 48 grams per 100 c c) or higher

Transfusions as a Means of Expediting the Return of the Blood to Normal

An example of a situation in which blood transfusions could be of help in accelerating convalescence would be in a patient with a bleeding peptic ulcer, in whom the medical treatment had been instituted and all evidence of blood loss had ceased It is known that under these circumstances with proper iron medication the hemoglobin will regenerate at the rate of about 1 per cent a day until the normal level is reached If, for example the hemoglobin is 50 per cent and the bleeding is controlled, then the blood would reach a normal level of 85 per cent in about 35 days If this patient were given 3 blood transfusions of 500 c c each within the few days following the control of the bleeding, each transfusion of 500 c c should increase the hemoglobin of the circulating blood approximately 10 per cent If these were administered every other day, the blood would reach 80 per cent within a few days and the patient s convalescence would be materially shortened On the other hand there is the possibility that thereafter such transfusions might depress the normal activity of the bone marrow for an unknown interval of time

At present in my opinion it can only be said that blood transfusions as a means of expediting the return of the blood to normal in anemias must be considered but there is not sufficient data at hand to prove how effective they are With the improved safety and the ease with which blood transfusions can now be given and the availability of donors as the result of the "blood bank' service it is possible that the use of blood transfusions for the purpose just discussed will be more general in the future

Use of Blood Transfusions in the Treatment of Anemia of Chronic Infections

Blood transfusions are of value in the treatment of chronic infections associated with anemia if for no other reason than the favorable effect they exert on the anemia itself Clinical experience has shown that they improve the general condition of the patient and with this it is a reasonable assumption to consider that the resistance to infection likewise is increased

In addition Pastore[1] has shown that, when dealing with the incidence of postpartum infection in patients with varying degrees of anemia there is a definite relationship between the amount of blood lost and the occurrence of infection Also it has been shown by Kolmer[13] that certain specific and non specific antibacterial and antitoxic substances may be transferred by transfusions of fresh blood or plasma and according to this investigator this may be of considerable value in the treatment of infections and infectious diseases Convalescent serums and immune globulins have proven successful in the treatment of such infections as scarlet fever measles mumps and pneumococcal infections

My own impression is that blood transfusions are unquestionably of value in combating an infection in the presence of an anemia and that probably they are also useful in the treatment of infections even in the absence of a reduction in the hemoglobin and red blood cells I do not believe however that the evidence is clear enough at present to advise the routine administration of either blood or plasma for this purpose in such patients This is especially true now that penicillin and the sulfonamides are available for the treatment of such conditions

Use of Blood Transfusions in Hemorrhagic Diseases

Blood transfusions are of value in controlling abnormal bleeding especially when it results from a deficiency of thromboplastin as in hemophilia from hypoprothrombinemia in diseases of the liver and from purpura It is useful also in a deficiency of fibrinogen in the circulating blood but this condition is so rare that it need be only mentioned

It is known that vitamin K is effective in all forms of hypoprothrombinemia except that due to liver disease In the latter condition blood transfusions are the only form of treatment which should be used when bleeding due to this cause is present Even in patients with normal hepatic function the latent period before vitamin K therapy proves to be effective may be prolonged and hence if the situation is urgent then a blood transfusion is advisable It should be kept in mind that prothrombin activity is lost in alkaline solutions and in blood and plasma at room temperatures It more slowly disappears in blood or plasma maintained at 4 C Plasma separated promptly from drawn blood and frozen immediately retains almost all of its prothrombin activity for several months Although prothrombin is preserved in desiccated plasma it may be destroyed during reconstitution if the reaction is not maintained near neutrality[14] Reconstitution of the desiccated blood plasma with a 0 1 per cent solution of citric acid instead of distilled water is said to keep the reaction at neutrality and preserve the prothrombin content satisfactorily

It has been shown that the plasma of normal blood contains a substance effective in reducing the coagulation time of the blood of patients with hemophilia to normal and that this fraction is associated with the globulin portion The material which is effective in the acceleration of the clotting process in hemophilia apparently is quite stable and is well preserved in blood or plasma kept at 4° C and in frozen and desiccated plasma[15]

In the management of patients with hemophilia the method of choice based upon the most extensive experience is to give citrated blood in amounts of 500 c c until the coagulation time approaches normal It will usually remain in such condition for several days during which interval even a major operation may be accomplished It is true that smaller amounts 50 to 100 c c may be

of some benefit but usually it is advisable to give larger quantities because the results are more decisive and prolonged Moreover transfusions are often given after profuse bleeding and hence the larger amounts will have a more favorable effect in replacing the red blood cells and hemoglobin which have been lost

It has been concluded by Johnson[16] that lyophile plasma which has been frozen and dried within a few hours after removal from the donor, decreases coagulation time in patients with hemophilia effectively and that thromboplastic activity is preserved in the plasma for at least 3 months when it is kept at 5° C

In the control of thrombopenic purpura citrated blood transfusions usually are effective, but I have observed refractory cases In idiopathic thrombocytopenic purpura the ultimate form of treatment usually is splenectomy, provided the diagnosis can be established with a certainty, and if the symptoms are severe enough to warrant such an operation During the active stage, when the operative mortality is high and in preparation for the operation, or if surgical treatment is refused, repeated blood transfusions of 500 c c each of fresh citrated blood should be given in an attempt to provide the necessary blood platelets It should be kept in mind that fresh blood and not that which has been stored in the blood bank probably is superior in its effects as in the latter the platelets are agglutinated after 24 to 36 hours and possibly are functionally ineffective

Treatment of Shock Associated with Hemorrhage

A comprehensive discussion of shock will not be attempted here, but I will present in a brief statement my own personal views on the treatment of shock with blood transfusions and various forms of blood substitutes

All agree that the major indication in the treatment of shock is to place something in the vascular system which will remain there and increase the blood volume In shock associated with hemorrhage 1 000 c c of blood should be given at the rate of about 500 c c per hour or faster, if the patient s condition is precarious In an emergency for example 500 c c may be injected within 10 minutes if the situation warrants it When substantial evidence of improvement appears, an additional 500 c c to 1500 c c should be administered at the rate of approximately 250 c c per hour depending on the level of the blood pressure on the patient s general condition and his response to therapy In acute hemorrhage it has been stated that transfusions should be withheld on the grounds that they might raise the blood pressure to the point where they would dislodge a clot and cause a resumption of the hemorrhage or augment the rate of blood loss which had begun to diminish Some years ago I abandoned this belief when I was unable to demonstrate to my satisfaction that the blood pressure increased to the point where it might be responsible for such a condition even

when transfusion was given at a fairly rapid rate If whole blood is not available for administration to patients with acute hemorrhage then serum or plasma or some form of blood substitute should be utilized although in my opinion these forms of treatment are of inferior value

In the treatment of traumatic shock without hemorrhage it would seem that the most satisfactory form of treatment is the injection of from 500 to 000 c c of citrated plasma or reconstituted desiccated plasma in equivalent amounts The use of desiccated human or animal bovine albumine and certain blood substitutes will not be discussed here If it is not possible to obtain plasma then it is advisable to inject whole blood although it has the disadvantage of adding red blood cells to the recipient s blood in which the red blood cell count is already above normal As the injected blood is more dilute than the blood of the recipient it will of course reduce the concentration of the blood of the latter to some extent

The Use of Blood and Plasma Transfusions as a Means of Providing Protein in the Blood Stream

In recent years the possibility that the blood proteins may be increased by the administration of blood intravenously in patients with hypoproteinemia has been emphasized When intravenous injections are given for this purpose however the essential part of the blood is the plasma The red blood cells are not only valueless for this purpose but often they are even objectionable The treatment of hypoproteinemia by means of the injection of blood plasma or substances derived from the plasma is a subject about which much valuable information is now being developed and hence no permanent conclusions can be drawn at present It is a field of endeavor however which holds definite promise for the future

Blood Blood Derivatives and Blood Substitutes Used for Intravenous Injections

Our knowledge in this field is growing so rapidly as a result of the impetus given to it by the investigations during World War II that opinions concerning various aspects of it change from day to day Hence anything which is said at present in regard to these therapeutic agents must be accepted as purely tentative and subject to revision as our present knowledge is evaluated and new information is added At this time I shall attempt only to list the various materials which have been employed for intravenous injection largely in the treatment of shock and to comment briefly on our present day tentative impression of their effectiveness

The following is a partial list of some of the substances now used for intravenous administration mainly for the treatment of shock, with and without hemorrhage

I Blood
  1 Unmodified
  2 Citrated
    (a) Fresh
    (b) Stored ("Bank" blood)
II Plasma
  1 Liquid citrated plasma
  2 Frozen
  3 Desiccated
III Serum
  1 Liquid
  2 Frozen
  3 Desiccated
IV Blood derivatives
  1 Albumin
    (a) Human
    (b) Bovine
V Blood Substitutes (partial list only)
  1 Isotonic solutions of saline and dextrose
  2 Acacia
  3 Casein derivatives (amino acid solutions)
  4 Isinglass
  5 Gelatine
  6 Ascitic fluid

It should be recognized that whole blood plasma either frozen or desiccated and human albumin have received the greatest general acceptance as the materials of choice to be employed in the treatment of hemorrhage or shock There is of course no substitute for whole blood in the treatment of anemia although there has been some discussion as to the value of whole preserved blood as compared to fresh citrated blood

The Blood Bank

There can be no question but what the use of the blood bank as a means of storing blood for transfusion purposes is of the greatest value in clinical medicine It has demonstrated its worth chiefly because (1) by such means an unlimited amount of tested blood is provided which is available immediately at all times

for the treatment of patients who require blood transfusions and (2) it makes possible the use of almost any amount of blood in patients for whom paid donors cannot be utilized Experience has shown that any hospital not having a blood bank is definitely handicapped in the treatment of many patients Hence all institutions should make every endeavor to establish such an organization at the earliest possible moment

Changes Which Occur in Red Blood Cells in the Blood Bank — Although it is feasible to preserve blood in a citrated solution for as long as 30 days in a refrigerator and then use it for a transfusion studies have shown the advisability of utilizing such blood within a period of 7 days after it has been drawn from the donor There is no good evidence to indicate that sodium citrate exerts a deleterious effect on the life of the erythrocytes in the circulation of the recipient when the blood is administered within a few hours after it is withdrawn from the donor[17] It is known however that 80 per cent of the erythrocytes stored in citrate solution alone for 7 days or longer are destroyed within 4 hours after they are injected into the veins of the recipient[19] It is not advisable therefore to use such blood for transfusion purposes It has been claimed by Ross[15] however that when red blood cells are stored in a glucose citrate mixture for two weeks there will be a survival of 80 to 90 per cent of the transfused erythrocytes in vivo for at least 48 hours after transfusion One of the most satisfactory mixtures employed for this purpose is a glucose-citrate solution buffered with sodium phosphate to a pH of 7 4 Fifty cubic centimeters of this mixture containing 3 5 per cent of sodium citrate and 5 per cent dextrose is a sufficient quantity for 500 c c of blood

It seems to have been clearly established that there is an inverse relationship between the length of time that red blood cells are stored and the interval which they survive in the circulation It must be concluded therefore that when blood is to be used in the treatment of anemia it should not be stored more than 7 days if the optimum results are to be anticipated After that time the red blood cells should be separated by centrifugation and discarded The plasma thus obtained then may be frozen or desiccated and utilized in conditions which do not require the presence of red blood cells such as shock

Effect of Storage on the Leukocytes — All investigators are in accord with the statement that the white blood cells begin to display the early changes of disintegration within 24 to 36 hours after the blood is drawn into a dextrose citrate solution and preserved under proper conditions of refrigeration Within 4 to 5 days these alterations usually progress to such a degree that an accurate differential white blood cell count is impossible It has been shown by Shamov[8] that phagocytosis is preserved to some extent in cadaver blood for as long as 11 hours Additional information in regard to the activity of the leukocytes is to be found in the studies of Karavanov[19] who observed that the neutrophils

retained some of their phagocytic ability after 5 or 6 days of storage, but that it declined sharply after the second day It appears certain therefore, that the time of survival of the leukocytes with the retention of their physiological function in stored blood is very brief From the standpoint of supplying white blood cells to the recipient for the purpose of combating infection, it is unlikely that blood transfusions are of value

The Blood Platelets in Bank Blood — In general it may be said that the evidence, which is available, indicates that there is rapid degeneration of the blood platelets in stored blood which probably makes them ineffective in the treatment of bleeding conditions such as thrombopenic purpura, in which there is a deficiency of platelets It has been shown by Drew and Scudder according to Strumia[70] that the platelet count falls to less than 100 000 per cubic millimeter within 24 hours in stored blood and to about 40 000 per cubic millimeter in 3 days Additional studies by Dubash, Clegg and Vaughan[71], however, indicate that the platelets remain at a fairly constant level of 40 000 per cubic millimeter even after 14 days of storage in a citrate dextrose mixture It must be concluded however that only fresh citrated blood should be employed as a therapeutic agent when it is desired to add functionally active platelets to the circulating blood of a recipient

As previously stated it is known that prothrombin is a labile substance which is destroyed rapidly in alkaline solutions and in blood and plasma when kept at room temperatures but it is lost less rapidly when maintained at a temperature of 4° C

A Brief Consideration of Various Other Types of Blood Substitutes

Two of the most satisfactory types of blood substitutes probably are dried and frozen plasma and at present they should be given first consideration of the many which have been suggested and tried in clinical medicine The use of frozen plasma should be considered especially by all hospitals that utilize a blood bank This is because the method of freezing is not complicated the material may be kept at low temperatures for an indefinite period of time, and finally the blood in the bank which is not used at the end of 7 days, may be centrifuged, the erythrocytes discarded and the plasma thus preserved for future use The same argument may be used for desiccated plasma The only difference is that in the case of the latter, a more complicated apparatus is necessary for its production, and this is not usually available in hospitals

Observations have shown that when liquid plasma, prepared by a careful closed technic is frozen at a temperature below − 20° C, it may be preserved indefinitely when stored below − 15° C In this state there is no loss of any

of the thermolabile elements such as prothrombin complement and plasma thromboplastin When the material is to be used it is advisable that thawing of the frozen plasma be done in a water bath at body temperature of 37° C with occasional shaking and that the restoration to a liquid state should not consume more than 30 minutes per bottle of plasma It is also recommended that a filter be placed in the transfusion apparatus when such plasma is administered to a patient in order to avert possible damage from particles of fibrin which sometimes are suspended in the solution

Dried plasma has been in universal use in the treatment of many thousands of our wounded during the last war and appears to have been the answer to the treatment of shock under conditions of mobile warfare although it does not by any means supplant the use of citrated whole blood in all instances When dried plasma is properly prepared and packaged it will remain in suitable condition for use better than any other form of blood derivative It is known to be stable at ordinary room temperatures but should not be permitted to freeze or stand at a temperature of 55 C or higher for any length of time There have been several papers published which report severe reactions attributed to the use of pooled plasma It is the opinion of Newhouser and Lozner[27] however after reviewing the literature and the results obtained from the use of plasma prepared at the Naval Medical School that the dangers from properly prepared pooled plasma are practically nil The same conclusion is reached by Thalhimer[23]

The place of frozen and dried plasma in civil life remains to be determined by an extensive survey of the results attained during the past war in a large number of cases and a final estimation of the need of such material in the average hospital or practice under the normal conditions of life

Other blood derivatives and substitutes which have been used or suggested for intravenous injection in place of whole blood are as follows blood cells from the blood bank[4] human type of O cells suspended in 10 per cent corn oil[5] liquid plasma[27] concentrated solutions of albumin[22] bovine albumin[6] gum acacia[7] amino acid mixtures[8] ascitic fluid[9] hemoglobin saline solutions[30] gelatin[31] isinglass[37] and pectin[33]

Selection and Protection of the Blood Donor

With the unprecedented donation of blood due to the demands for the wounded during World War II and in meeting the needs of the civilian blood banks an excellent opportunity has been afforded to accumulate data on the effect of the removal of approximately 500 c c of blood at one or more intervals on the health of the donors who were used for this purpose

In determining the suitability of the donor no better criteria can be employed

than those established by the American Red Cross for the purpose of collecting blood to be used by our wounded[34] From the experience of those in charge of this project the matter of eligibility is best determined on the basis of a few simple tests and a series of questions rather than a complete physical examination I concur that this is undoubtedly the most feasible plan to pursue

For the full details of the experience of selecting donors for the American Red Cross the comprehensive publications of Heiss and Taylor[34] and Boynton and Taylor[35] should be consulted The following regulations have been in force by the Red Cross during the war (1) donors between the ages of 21 to 60 are employed, although those under the age of 21 may be used if the written consent of the parents is obtained, (2) donations are given not oftener than every 8 weeks and no more than 5 donations are permissible in any twelve month interval, (3) no donor is accepted if the oral temperature is greater than 99 5° F, (4) a donor is not accepted unless his hemoglobin level is 80 per cent or higher (5) the systolic blood pressure must be between 100 and 200 millimeter of mercury, (6) a note is made concerning any abnormalities of the pulse, (7) it is probably a wise policy to reject all prospective donors who have hay fever or any of the common allergies (8) if any acute infection has been present within the past 6 weeks a person is considered to be unsuitable for donating blood, (9) of great importance is the rejection of all persons, who give a history of having had jaundice, or if a case of jaundice has been present in their immediate family for the past year The data regarding the importance of this contraindication to serving as a donor is summarized in an editorial in the New England Journal of Medicine[36] (10) likewise the transmission of malaria by infected blood donors should always be kept in mind and all persons who give a history of having had the disease within the past 15 years should not be employed

The transmission of syphilis deserves special comment Even when every precaution is taken to prevent this disease there still remains the remote possibility that it may be acquired in this manner All donors should be asked if they have ever had the malady and a serological reaction for the condition should be employed without fail In conditions requiring an emergency blood transfusion then tested bank blood or serum can be utilized, and if it is necessary to use fresh blood then an emergency serological test for syphilis should be made obligatory It is remotely possible that the disease might be transmitted through a blood transfusion even though a person honestly denies all knowledge of having acquired it there is no evidence of it on physical examination and in the presence of a negative serological test for the disorder For example this might occur in persons who were in the prechancre stage of syphilis for there is evidence to show that the blood in this phase of the malady is infectious Such a statement is supported by the report of Frazier and Pian[37] who found that in one of their patients the blood stream was invaded by the *Treponema pallidum* at least 20

days before the appearance of the chancre and in addition the proof of syphilis was complete because the living organisms of the disease were isolated from the blood stream of the patient by animal inoculation Hence it must be kept in mind that in exceedingly rare instances it is possible for a person to transmit syphilis by a blood donation regardless of the fact that all evidence of the disease is lacking It has been determined that in the processing of desiccated plasma and albumin fortunately the *treponema pallidum* is destroyed and in storage under conditions present in the blood bank the organisms undergo progressive deterioration in citrated whole blood With this there is a corresponding reduction in the risk of transmitting the disease by such blood and it is probable that when it remains under the proper conditions of refrigeration for 4 days or longer the risk of transmission is practically nil[28]

Blood Transfusion Reactions

The main causes of severe untoward effects of blood transfusion have been largely eliminated with the knowledge of the blood groups resulting from the studies of Landsteiner in 1901 and the introduction of citrated blood for trans fusion purposes by Hustin[29] Agote[1] Lewisohn and Weil[3] in 1914 and 1915 Improved technic has now reduced the incidence of such reactions to the vicinity of about 6 per cent even when all of the minor unfavorable effects are included If such complications occur more commonly than this figure then a careful sur vey of all possible causes for this undesirable and unnecessary situation should be determined There does not appear to be an increased number of unfavorable effects when stored blood is used as the number of reactions approximate those which follow the use of fresh citrated blood

Nature of Blood Transfusion Reactions

The untoward results which follow the intravenous injection of blood may be classified as follows

I Reactions due to hemolysis of blood resulting from
1 The accidental use of the incompatible main groups (A B and AB)
2 The transfusion of blood with incompatible subgroups
3 The Rh factor
4 The use of group O as a universal donor
5 The use of blood which has been stored too long
6 The transfusion of blood in patients with hemolytic anemias

II Reactions due to non specific factors resulting from
  1 Toxicity of the citrate
  2 Use of unclean apparatus or contaminated solutions
  3 Allergic manifestations
  4 'Speed reactions
  5 Embolic phenomena

Hemolytic Reactions — Fortunately these reactions, which are much more serious than the non hemolytic types are far less frequent, as they are observed in less than 0 5 per cent of the patients who receive blood transfusions With the increased knowledge of the causes of these unfavorable effects it is likely that they will occur even less frequently in the future Nevertheless in any institution where blood transfusions are given frequently, the occurrence of a hemolytic reaction with perhaps a fatal termination is always a possibility which must be kept in mind Hence all safeguards must be maintained to avert such a tragic possibility

The immediate symptoms of such a reaction are severe lumbar pain flushing and burning of the face a sensation of tightness and constriction in the chest and chills with some degree of collapse It is of interest to note that following an incompatible transfusion a majority of the donor's cells are eliminated from the circulation within a few hours after they enter the vascular system of the recipient In some instances it is possible to discover clumps of agglutinated cells in the blood sample withdrawn from the recipient and these may persist in vivo for 24 hours

If a sufficient amount of blood is hemolyzed the subsequent course of events are hemoglobinemia, hemoglobinuria jaundice ominous general symptoms, oliguria anuria uremia and death With the rapid destruction of erythrocytes and the liberation of hemoglobin there is a transformation of the latter into an excess of bilirubin If this change is slow enough then the excess of bilirubin is eliminated in the bile, and only slight jaundice results On the other hand if blood destruction is rapid, this cannot be accomplished and the jaundice is more intense It is also likely that damage to the liver might result and hence a 'toxic factor may be responsible for the jaundice in some instances

Although the blood bilirubin peak resulting from the increased destruction of blood is reached within 5 or 6 hours after the process begins obvious jaundice is not likely to be observed until the end of approximately 12 hours as time is required for the staining of the tissues Once the blood destruction is completed the bilirubin concentration falls rapidly and usually reaches normal limits within 2 or 3 days It is not common for jaundice of this nature to persist for longer than 2 or 3 days

The most serious complication of intravascular hemolysis is some degree of

renal failure which is considered to be the cause of death when it does occur The theory that this is due to blockage of the renal tubules with acid hematin[40] a relatively insoluble compound of hemoglobin which is formed only in acid urine is no longer tenable[41] It is now generally thought that the renal insufficiency is due to degenerative changes in the renal tubules as a result of some nephrotoxic factor When severe renal damage occurs there may be no evidence of it for the first 2 or 3 days after the incompatible transfusion has been given After this asymptomatic latent period however the general symptoms appear and usually between the sixth and twelfth days the patient becomes comatose and succumbs or at this time he may begin to secrete large quantities of urine and recovery follows[4]

Cause of Hemolytic Reactions — In brief it may be stated that agglutination and destruction of the donor s red blood cells may occur under the following conditions

I As the result of an occasional tragic error in which incompatible cells are mistakenly given to the recipient Considering the large number of blood transfusions which are given this is a rare accident Nevertheless as long as humans err the possibility that it may happen occasionally must be anticipated The seriousness of such a mistake is apparent when one considers that death occurs in over one half of the patients who receive 500 c c of incompatible blood

II Patients who are negative from the Rh factor standpoint may have serious and sometimes fatal reactions It is now known that in clinical medicine this factor is of importance in at least 3 conditions namely (1) in pregnant women (2) in infants with erythroblastosis fetalis and (3) in patients receiving repeated blood transfusions It is only in patients in whom there is a negative Rh factor that there is danger of transfusion reactions on this basis In a woman who has a negative Rh factor serious difficulty may arise if she should become impregnated by a male who has a positive Rh factor In this event the fetus may be Rh positive and as a result the formation of anti Rh factor antibodies may occur in the maternal organism These apparently may be transmitted through the placenta and hemolyze the red blood cells of the fetus thus producing the condition known as erythroblastosis fetalis For further details concerning this condition the section dealing with this disease should be consulted Furthermore in such a pregnant woman with anti Rh antibodies in the blood there is a danger that she may be transfused with positive Rh blood and these erythrocytes would be hemolyzed If a male or female is Rh negative and should receive repeated blood transfusion with Rh positive blood which would stimulate the formation of anti Rh antibodies then following the third or possibly the fourth such transfusion the anti Rh antibodies may have reached such a titre that the donor s erythrocytes would be hemolyzed The only safe procedure to avoid reactions associated with the Rh factor is to type the blood of all pregnant women

and both males and females who are to receive repeated blood transfusions, and if they fall into the Rh negative group, then only Rh negative blood should be administered to them

III The use of the universal donor The majority of those who have investigated the matter of utilizing type O blood for transfusion of all recipients regardless of their blood type do not consider it to be a dangerous practice In large numbers of such patients who have received group O blood, the reaction rate has not been greater than when the type specific blood is employed It should be kept in mind however, that type O serum agglutinates the red blood cells of all other groups If type O blood is injected slowly, however, the donor s serum becomes so diluted with that of the recipient that agglutination and hemolysis ordinarily do not occur In rare instances, however, the titre of the donor s serum may be so high, above 1–32 that the desirable dilution is not accomplished and hemolysis may result This is such a rare condition, and as the blood is usually given slowly, severe hemolytic reactions are not encountered commonly due to this cause

IV The use of blood which is stored too long in the blood bank In general experience has shown that it is not advisable to use blood which has been removed from the donor longer than 7 days This is because apparently such cells become more fragile and may be hemolyzed to a certain extent by the recipient s serum

V The transfusion of blood into patients with various types of hemolytic anemias It has been noted that severe and even fatal hemolysis may occur when blood transfusions are given to patients with severe hemolytic anemias even though all precautions have been taken in matching the blood of the donor with that of the recipient Although this hazard is always a possibility nevertheless in such patients blood transfusions have been given with safety They should however be administered always with extreme caution Even though cross matching indicates that the blood is compatible, the first 100 c c of blood should be administered slowly and the injection stopped immediately, if the slightest evidence of a reaction occurs

Blood Groups

Since the epoch making contributions of Landsteiner[43, 44] and his pupils in 1900 and 1901 in which the red blood cells of humans were grouped for the first time into four types the safety of transfusing the blood of one person into another has been assured except in a small number of instances which have to do with the various sub-groups and the Rh factor

The fact that the blood of all individuals can be divided into four types depends on two different red blood cell characteristics called isoagglutinable substances or agglutinogens which have been designated by the letters A and B

These characteristics may be present in the erythrocytes either singly or jointly or they may be absent If they are absent the red blood cells are designated as type O There are therefore four types of erythrocytes namely groups O A B and AB

When group O corpuscles are present in the blood of a person they are of the type which are not agglutinated by either the agglutinins A or B and therefore they may be introduced into the blood of any person without being agglutinated then hemolyzed and hence destroyed For this reason persons having red blood cells of this type are called universal donors It should be noted however that the agglutinins A and B are present in the serum of an individual with group O corpuscles and hence such a serum will agglutinate the red blood cells of all persons except those who have O groups namely groups A B and AB corpuscles will be affected

A patient with group A corpuscles has anti B serum and one with B corpuscles has anti A serum whereas a person with group AB red blood cells has neither anti A nor anti B serum

From a practical standpoint of transfusing blood into a patient the essential information to obtain is that the red blood cells of the donor will not be destroyed by the serum of the recipient This would not only nullify the purpose of the blood transfusion by destroying all of the transfused cells but would result fatally in about one half of the cases where 500 c c or more of incompatible blood has been given It is not so important to determine if the serum of the donor will agglutinate the red blood cells of the recipient This is because the donor s serum is so diluted by that of the recipient that the destruction of the recipient s cells usually does not occur to an important extent

The Incidence of Various Blood Groups

The following table gives the incidence of the four main blood groups as shown from data collected by various observers

Blood Group	Schiff and Boyd[4] Per Cent	Snyder[46] Per Cent.	Barton Per Cent	Mos Designation
O	40	45	4	IV
AB	5	4	4	I
A	40	41	39	II
B	10–15	10	12	III

The following table shows the presence of the various agglutinins in the serum

Red Blood Cell Group	Agglutinins in the Serum
O	Anti A and anti B
A	Anti B
B	Anti A
AB	None

Use of this information is made in the typing of unknown red blood cells by using test serum B (anti A) and test serum A (anti B) typing sera of high titre If the unknown red corpuscles are agglutinated by B (anti A) they are type A if they are agglutinated by A (anti B), they are type B, if they are not agglutinated by either, then they are type O, and if they are agglutinated by both, they are type AB

Although there are four main varieties of human erythrocytes now distinguishable serologically, there are many sub groups whih greatly increase the number For example, there are 8 classes of the A B system 5 classes of the M N system, 2 classes of the P system and at least 5 types of the Rh agglutinogens[49] Hence there would be theoretically at least 40 different kinds of human blood which could be distinguished by serological reactions This is indicated by multiplying the figures given above, namely $8 \times 5 \times 2 \times 5 = 400$

Prevention of Hemolytic Reactions

As hemolytic reactions may result fatally it is important to take all measures calculated to prevent their occurrence The following procedures are recommended for this purpose

1 The sera employed for blood grouping must be of high titre and rapid acting Anti A serum must be capable of agglutinating the sub groups of A and AB

2 In each instance the blood cells of both the donor and the recipient should be typed and cross matched

3 The test tube technic of matching should be used and the material permitted to stand at room temperature for 2 hours according to the recommendations of the Blood Transfusion Research Committee of Great Britain if it is possible to delay the transfusion for that period of time Furthermore it is of assistance in excluding the Rh factor to incubate the preparation at a temperature of 37° C for 30 minutes In addition it is recommended by Barton[47] that the following rules be observed with respect to the Rh factor if these reactions are to be prevented Routine typing for the Rh factor should be carried out in the following patients

1 Those who are likely to receive repeated blood transfusions
2 Those who give a history of having had reactions following previous transfusions
3 Those who have had an emergency transfusion and in whom a second one is to be given
4 All obstetrical patients before admission to the hospital no surgical deliveries should be undertaken unless such patients have been so typed
5 All infants born with jaundice and anemia in order that their recovery may be facilitated by transfusions with Rh negative blood

It is my opinion that even though the Rh factor is a poor antigen and only about 13 per cent of the white population is Rh negative the hazards associated with the transfusion of Rh incompatible blood are such that Rh typing should be made a routine procedure in all patients prior to transfusions It is my belief therefore that the avoidance of Rh incompatible reactions can be ensured only by testing each patient who is to receive a blood transfusion for the Rh factor If it is found that they are Rh negative then only Rh negative blood should be administered This type is not always available but a special list should be kept by every hospital of such donors as well as their Landsteiner group It may be necessary to give an Rh negative group O blood to some patients but in my opinion this is preferable to giving an Rh positive blood of the same general type to a patient who is negative

Treatment of Patients Who Have Received Incompatible Blood

When death does occur as the result of an incompatible blood transfusion it is usually due to severe impairment of renal function This is evidenced by anuria an increase in the non protein nitrogen of the circulating blood and a uremic state Regardless of whether one believes that this results from a blockage of the renal tubules with acid hematin or from degeneration of these tubules there is general agreement that the urine should be alkalinized promptly in the treatment of such a complication It is recommended by Ross[50] that sodium citrate be given intravenously because solutions of the drug usually are available in hospitals where transfusions are given From 100 to 200 c c of a 2 5 to 3 0 per cent solution of the drug should be given intravenously at a slow rate This should produce alkalinization of the urine in about 15 minutes[51] The same result may be attained by the intravenous administration of 500 c c of a one sixth molar solution of sodium lactate or a 4 to 5 per cent solution of sodium bicarbonate Sodium bicarbonate then may be given orally in an initial dose of one teaspoonful (40 grams) 4 times daily thereafter until all danger of renal damage has passed

Experience has shown that blood should be injected into the veins of the

recipient slowly It is usually advisable to give 250 c c to 600 c c per hour Or if it is suspected that a severe hemolytic reaction may occur, then only 50 c c of blood should be given, and no more blood injected for one hour in order to determine if hemolysis of the donor's cells has occurred The destruction of such a small amount of red blood cells by the recipient usually will produce symptoms but will not cause a fatal result

A Consideration of Non Hemolytic Reactions

'Speed" Reactions

In my opinion there are two types of "speed reactions The one which occurs rarely is due to the sudden overload of the vascular system in patients with a diseased and weakened myocardium The other, which is common, is associated with the production of a febrile reaction In regard to the former type it may be said that it has long been known that intravenous fluids cannot be administered rapidly to patients with a weakened heart muscle as there may follow all of the manifestations of acute congestive failure Ordinarily the rate of injection should not exceed 10 c c per minute or 600 c c per hour, and in some instances it should not be greater than 5 c c per minute although it is possible in severe cases of shock in which death appears to be impending, to give 500 c c of blood or plasma in 10 minutes

In addition to the possibility of overloading the heart I am convinced that the rapid administration of blood or plasma may be followed by a febrile reaction This may be explained on the following basis If pyrogenic bacteria or their products are present in relatively weak concentrations, a febrile reaction will not result when the fluid is given slowly On the other hand the same concentration of pyrogenic material may be responsible for a severe febrile reaction if the fluid is administered at a more rapid rate In my earlier experience in giving blood transfusions a quarter of a century ago, the blood was injected from a container under pressure and as much as 500 to 800 c c was given in 20 minutes Our rate of chills and fever with such a technic varied from 40 to 60 per cent which was unbelievably high In the past 10 to 15 years or more all blood transfusions on my service have been given at a much slower rate by the gravity method As a result the incidence of reactions varies between 4 and 6 per cent I am convinced that the reduction in the rate of injecting the citrated blood accounts in large part for this gratifying diminution in the reaction rate

Pyrogenic Reactions

It is estimated that contamination with pyrogenic bacteria and their products accounts for 2 to 5 per cent of the reactions when citrated blood is given intra

venously Since the initial work of Seibert[5] bacterial contamination has been recognized as one of the most common causes of febrile episodes following intra venous injections with either crystalline solutions with whole blood or with plasma The reader is referred to the publication of Strumia McGraw and Blake[53] for a practical discussion of how such common and annoying reactions may be averted by the proper preparations of distilled water and cleansing of all rubber tubing and glassware

The nature of such a reaction is fairly constant It usually manifests itself within 15 to 30 minutes after the intravenous injection has been given with a chilly sensation or outspoken chill and increased temperature Often associated with this there is a sense of malaise and nausea The reaction usually subsides within a few hours and rarely persists longer than 8 hours In no instance has such a condition terminated fatally in my experience but the associated symptoms may be so severe and enervating as to have a very deleterious effect on the patient

Reactions of an Allergic Nature

Reactions on the basis of allergy occur in about 1 per cent of the recipients following blood transfusions They are usually in the nature of a mild urticaria but in some instances attacks of true bronchial asthma angioneurotic edema or outspoken anaphylactic shock may occur It is probable that these manifesta tions result from the injection of blood drawn from a donor who was not in a fasting condition that is food had been taken within 4 to 6 hours before the blood was obtained In the blood of such patients there undoubtedly might be sub stances present to which the recipient was sensitive and these could produce allergic symptoms This complication might be eliminated if it is required that all donors be in the fasting state This is not always feasible nor are the reactions of such a nature that life is endangered when such a requirement is not often enforced Furthermore the subcutaneous injection of 0 3 to 0 5 c c of 1 1 000 solution of epinephrin chloride will at once control such manifestations when they do occur It does not seem necessary therefore to demand without exception that the donors for blood transfusions be in the fasting condition

Possible Toxic Effects of Sodium Citrate

When sodium citrate was first introduced as an anticoagulant it was customary to give only 500 to 800 c c of blood over a period of 36 to 48 hours or longer and hence the possibility that the substance might be toxic was not thought to be possible In more recent years since the introduction of the blood bank it has become commonplace to give much larger amounts of blood especially in post operative shock so the matter of toxicity of the drug must be re-evaluated

This problem has been studied recently by Bruneau and Graham[54] who observed that dogs bled repeatedly, when given transfusions with citrated blood survived a shorter time than the control animals who received heparinized blood The clinical implication was that too large amounts of sodium citrate should not be injected as an anticoagulant in a short period

In my own experience there has never been the slightest suggestion that citrate can be considered in the least harmful when given in amounts which are ordinarily employed in blood transfusions of average amounts The possibility that larger quantities might be deleterious however, must be considered In a patient reported by Bruneau and Graham[54] 4,000 c c of citrated whole blood containing 14 0 grams of sodium citrate, was given over a period of 6 hours The unexpected death of the patient led them to suspect that the drug might have been responsible

As the ordinary transfusion of 500 c c of blood contains only 1 75 grams of sodium citrate it is unlikely that it could possibly be injurious It has been shown by Neuhof and Hirshfeld[55] that as much as 6 to 8 grams of this chemical may be injected intravenously in a ten minute period without producing symptoms and much larger quantities can be given over a longer interval without ill effects Apparently the drug is rapidly oxidized and excreted so that a large percentage is eliminated from the blood stream within a short time

Embolic Reactions

Although it is generally assumed that any particulate matter which will pass through the needle (usually 19 gauge) used for intravenous injections will do no particular harm to the patient, this is not entirely true When preserved plasma or blood is administered, the fluid should be filtered immediately before use for at least two reasons First, because at least one fatal case has been reported[56] following multiple pulmonary emboli which apparently had their source in fibrin particles present in liquid plasma, and second because such particles cause considerable annoyance in clogging the needle and delaying the transfusion, often much to the patient s discomfort

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STERNAL PUNCTURE

The introduction of sternal puncture and a study of the material thus aspirated from the marrow cavity has been of distinct assistance in the diagnosis and understanding of various hematological disorders It is estimated[1] that it furnishes information of clinical value in about two thirds of the cases and that the actual diagnosis may be made by this means in approximately 16 per cent of the patients when this cannot be accomplished otherwise In general it may be said that specific diagnostic information is obtainable in the following conditions

1 Leukemia, especially in acute and chronic subleukemic types
2 In the presence of a megaloblastic marrow, which is characteristic of pernicious anemia in relapse and also in closely allied states such as sprue certain deficiencies of the extrinsic factor and gastrointestinal disturbances (total gastrectomy intestinal stricture and anastomoses)
3 Agranulocytosis in the stage of maturation arrest
4 Neoplasms multiple myeloma and metastatic malignancies
5 Lipoid histiocytosis
6 Malaria
7 Leishmaniasis (kala azar)

It should not be assumed that the conditions named above always give a characteristic picture for in some instances the findings may be atypical and confusing In others the marrow may appear to be entirely normal even when other information indicates clearly that a certain blood disease is present One obvious explanation of this is that there may be an error in sampling of the marrow Furthermore it is known that treatment such as administration of liver extract to patients with pernicious anemia may be responsible for extremely rapid changes in the appearance of the marrow and finally it must be recognized that the interpretation of the findings in the material aspirated by sternal puncture requires considerable training and experience in order to evaluate them properly It is certainly a much more complex situation to interpret than a blood film and hence attention should be paid to the results of observation on the sternal marrow in direct proportion to the experience and ability of the person who has made the study It should be kept in mind moreover that positive findings in the bone marrow as a rule are more reliable from a diagnostic standpoint than negative ones athough in some instances the latter are of great importance

It is considered by Propp and Schwind[1] that in certain disorders there is a non specific picture in the bone marrow and while such changes are not absolutely conclusive from the standpoint of diagnosis they nevertheless provide useful information The following diseases are listed in this latter group poly

cythemia hypochromic hemolytic and aplastic anemias and myelophthisic anemia such as occurs in Hodgkin s disease

In my own opinion sternal puncture is of definite value in all patients with any type of blood disease In a few conditions it is by itself diagnostic but more often it is confirmatory of the clinical diagnosis which has been suggested and supported by other accepted diagnostic studies A real danger as previously suggested is that too much reliance may be placed on findings from sternal aspiration when they are reported by an inexperienced observer

It has long been known that the state of the peripheral blood does not necessarily reflect the true condition of the bone marrow and for this reason it had been the hope of clinical hematologists that a simple and reliable procedure might be devised one which could be repeated at intervals which would enable them to obtain more specific information concerning the nature of the bone marrow during the life of the patient Ghedini in 1908 trephined the tibia and obtained marrow for diagnostic purposes and bone marrow puncture for diagnostic purposes was introduced by Pianese in 1909 It was not however until 19 7 that Arinkin[3] introduced sternal puncture and hence made available a most valuable and practical method of diagnosis in hematology An excellent bibliography relating to the development of the method of sternal puncture and the evaluation of the information thus obtained is to be found in a comprehensive article by Segerdahl[4]

It should be kept in mind that when sternal aspiration is employed it is recognized that the specimen is diluted to a certain extent by blood and hence this must be taken into account when the findings are interpreted During the past few years however so much experience has been accumulated that much valuable information may be obtained by this means despite the mixing of the peripheral blood with the contents of the marrow cavity

Technic

The operation of sternal puncture is so simple that it can be performed a number of times if necessary in the same patient without undue discomfort and in all patients in whom the diagnosis of the blood condition is obscure

It is known that the sternal marrow remains active throughout life and that it is one of the most sensitive areas to respond to stimuli which cause changes in the marrow It is claimed[5] that simultaneous aspiration of marrow from several bones (ribs sternum pelvis) yields similar information Evidence has been obtained by von Domarus[6] however that some irregularity exists in the distribution of the cells of the sternal marrow and there is some confirmation of this at necropsy

The technic of accomplishing a sternal puncture successfully is a very simple

matter, and it does not result in an important inconvenience to the patient, although some slight pain is always associated with the procedure The puncture is accomplished with a short (about 3 to 4 centimeters) number 18 gauge lumbar puncture needle which may be equipped with a finger grip For 5 or 6 years we have employed such a short needle with a beveled obturator The needle is inserted in the midline of the body of the sternum about the level of the second intercostal space This site may be located readily by using the sternal angle as a guide, which indicates the level of the second rib It is advantageous to hold the lateral margins of the body of the sternum between the thumb and forefinger of the hand, which is not used for the puncture, as a means of approximating the center of the sternum This is of some importance because if the puncture is made too far laterally, the marrow cavity may not be entered

The puncture is made following novacaine infiltration of the skin subcutaneous tissues and periosteum of the sternum The outer table of the sternum is passed through at an angle of about 45 degrees with a firm boring motion and a "give" may be felt in some instances when the needle enters the marrow cavity When it is thought that the marrow cavity has been entered, the obturator is removed and an attempt is made to aspirate a small amount of material If this is not successful, then the needle should be pushed a short distance further and the process repeated until sternal marrow is obtained which has the gross appearance of normal blood In most instances there is a certain amount of sharp but transient pain when the marrow is aspirated

It is advisable to withdraw only about 0 2 to 0 5 c c of marrow fluid as this is a sufficient quantity for all studies and the collection of a greater amount means an increased dilution with the circulating blood which impairs the value of the examination somewhat Smears are made by ejecting the material from the needle of the syringe on to properly prepared cover slips It is usually advisable to make 10 or 12 smears from each specimen for despite careful technic perfect preparations are difficult to obtain This is because considerable experience is required to estimate the optimum size of the drop of blood and marrow mixture and because the material always contains a certain amount of fat The films thus prepared are stained with Wright's or Giemsa's stain

The method of staining marrow films, as used at the Simpson Memorial Institute, is as follows

1 Cover the marrow film with undiluted Wright's stain for one minute

2 Dilute with fresh redistilled water (pH about 6 6) in proportion of two drops of water to one drop of stain The amounts of stain and water may be varied depending on the quality of the stain The red blood cells should be stained pink and the nuclei of the white blood cells purple After 3 minutes the precipitate should be flooded off from the surface with distilled water The water should remain in contact only until the stain is pink

3 Cover the stained film with redistilled water add an equal amount of Wright s stain mix and stain for 3 minutes flood off precipitate and dry

By employing a specially devised instrument designed by Turkel and Bethell[7] it is possible to obtain a small amount of sternal marrow as a biopsy specimen and with the instrument reinserted about 1 cm below the original puncture to secure also the desired quantity of aspirated material

Examination of the Bone Marrow

As the aspirated material from the sternum is not homogenous like blood it is not possible to study it quantitatively with exactness It is possible however to make qualitative studies of the material just like tissue and to some degree rough quantitative determinations In the opinion of many who have studied the problem the range of cells in the marrow which have been given as normal is so great that they are useless On the other hand there is little doubt but that the degree of cellularity of the puncture fluid is of significance and some method of estimating the number of cells approximately is desirable It is recommended by Scott[8] that the cellularity be graded into (1) low (approximately the distribution of cells as observed in a normal blood film) (2) medium (that of a healthy marrow) and (3) high It is his opinion that to strain after greater preci ion i to attempt to endow the method with an accuracy it cannot possess

There are several other points in regard to the study of the aspirated sternal marrow which should be evaluated in addition to estimating the number of cells Attention should be directed toward the proportion between the white blood cells of all types and nucleated red blood cells which is normally considered by some to be in a ratio of 5 to 1 and by others 3 to 1 In anemias the ratio is much lower and may be reversed It is known also that normally the proportion of granular to nongranular white blood cells is about 4 to 1 Furthermore it should be kept in mind that some observers do not believe megaloblasts to be present in normal marrow and certainly all agree that if present their numbers are exceedingly small In pernicious anemia and allied macrocytic anemias however megaloblasts make up a considerable number of the nucleated cells and this constitutes the chief change in the marrow in these disease states

Normally in the bone marrow the cells multiply by karyokinetic division and ordinarily one sees a small number of mitotic figures It is important to estimate the number of mitotic figures for when they are increased it is indicative of some pathological condition It is estimated by Japa[9] that in each 1 000 nucleated cells about 15 normally show these evidences of cell division Changes in the number of cells exhibiting mitosis are observed especially in pyogenic infections and in the leukemias

Sternal Marrow in Patients with Acute and Chronic Hemorrhage

Following the sudden loss of a significant quantity of blood both the erythroblastic and myeloid elements of the sternal marrow show hyperplasia, especially the former There is an increase in the number of normoblasts and the reticulocytes Mitotic figures are observed to be more frequent than normal but such changes occur at the normal level of cell development Megakaryocytes are increased in number

In chronic hemorrhage with a resultant iron deficiency there is an increase in active erythropoiesis The degree of this change is dependent upon the severity and duration of the anemia In some instances there is a moderate increase in the cellularity of the marrow and many mitotic figures of the normal type may be present The number of reticulocytes are fairly numerous but not as great as observed following the acute loss of blood

The myelocytes are approximately normal in number There is no increase in the number of normoblasts following iron therapy which is interpreted to mean that iron is necessary for the completion of the final stage of erythropoiesis but not as a stimulus to the formation of normoblasts

Sternal Marrow in Pernicious Anemia

The cellularity of the marrow of patients with pernicious anemia in relapse is increased and the relatively great number of megaloblasts present in the material is striking The megaloblasts and promegaloblasts may make up from 45 to 65 per cent of all the nucleated cells which are present There is also an increase in the number of normoblasts, but this is a less distinctive alteration The megaloblastosis is interpreted as a maturation arrest at the megaloblast stage

Also increased are the hemocytoblasts which are cells with basophilic cytoplasm devoid of granules and with a nucleus which is denser than that of the hemohistioblast although they have the same reticular structure The latter cell is regarded by some as the most primitive stem cell of the entire hemopoietic series In a hyperplastic marrow due to any cause these cells are increased in number Hence they are observed in the bone marrow of patients with pernicious anemia during relapse in normoblastic marrow hyperplasia and in leukemic marrow In general however it may be said that in patients with pernicious anemia the characteristic findings in the films is the presence of many promegaloblasts and basophilic megaloblasts which frequently show mitotic figures

There is also a leukoblastic reaction of a non specific kind as indicated by an increase in the number of promyelocytes and myelocytes which are present This does not correlate on first thought with the leukopenia and relative lympho-

cytosis of the peripheral blood but the obvious explanation is that although the leukopoietic tissues in the bone marrow show signs of hyperactivity for some unknown reason the leukocytes are not released from the marrow at an increased rate It is of interest to note that the macropolycyte with hypersegmentation of the nucleus is often seen in the bone marrow of patients with pernicious anemia as well as in the peripheral blood

With the beginning of a spontaneous or a therapeutically induced remission there are very prompt and characteristic changes in the bone marrow The earliest detectable alteration which begins within 24 hour after treatment has been instituted is an increase in the rate of maturation of the megaloblasts This is shown by a decrease in the number of promegaloblasts and basophilic megaloblasts they promptly diminish in number and finally disappear entirely They are replaced by polychromatic and orthochromatic megaloblasts and this change is followed by the appearance of a large number of normoblasts The increase in the number of these cells reaches a maximum at the time the reticulocytes have attained their peak in the peripheral blood Simultaneously with alterations in the red blood cell forming elements there is a return of the granulocytic cells to normal as indicated by a rapid maturation of the abnormal myelocytes and other immature white cell forms which are replaced by normal cells

In the anemias which are closely related to pernicious anemia such as sprue the anemia due to a decrease in the extrinsic factor and others information concerning the changes in the bone marrow is not as abundant as in pernicious anemia All indications are however that the alterations are similar to those occurring in pernicious anemia both during relapse and in remission

Sternal Marrow in Chronic Hemolytic Anemia

In this condition there is extreme activity of the bone marrow elements as indicated by the greatly increased cellularity About 75 per cent of the marrow cells are nucleated red blood cells at the normoblast stage although a few are as young as promegaloblasts The variety of red blood cells which may be found in this type of marrow varies from the mature normoblast to the younger cell of the series with a basophilic cytoplasm which constitute the majority of the cells present Reticulocytes are observed in greatly increased numbers Granulopoiesis is normal

There does not appear to be any correlation between the changes in the bone marrow and the level of the red blood cell count in the peripheral blood This perhaps is because the production of the red blood cells is proceeding constantly at an excessive rate which means that the marrow will be found at each examination to be hyperplastic The level of the red blood cell count on the other hand may be more closely correlated with red blood cell destruction These two factors

which operate independently, could account for the discrepancies between the findings in the bone marrow and the peripheral blood

Sternal Marrow in Sickle Cell Anemia

The principal bone marrow changes in this condition are similar to those found in any hemolytic anemia, namely the presence of an excessive number of nucleated red blood cells Usually they average between 50 and 75 per cent of all the cells in the marrow The predominating variety is the normoblast Megaloblasts are not seen The only difference between the marrow of this type of hemolytic anemia and other varieties is the presence of sickle cells

The Sternal Marrow in Erythroblastic Anemia

The bone marrow in this condition is similar to that of patients with hemolytic anemia Nucleated red blood cells myelocytes and megakaryocytes are numerous Phagocytes are present and may contain iron pigment 'Foam" cells are said to be present in small isolated groups

Sternal Marrow in Aplastic Anemia

In true aplastic anemia the bone marrow fails in its functions of producing red blood cells white blood cells and megakaryocytes Aplasia of the red blood cell forming elements alone rarely if ever occurs In patients with idiopathic aplastic anemia it is to be expected that the bone marrow will show a striking reduction in all of the cellular elements which accounts for the formation of the red blood cells the white blood cells and the platelets of the circulating blood In the histological examination of the marrow of such patients often there is just such a picture, namely a fatty marrow with slight if any evidence of the cells which are responsible for the production of almost all of the formed elements of the circulating cells In recent years however, it has been recognized[10] that although the peripheral blood may show the typical changes of aplastic anemia the bone marrow may be normal or actually hyperplastic In such patients there may be some evidence of this such as an increase in reticulocytes of the circulating blood It has been emphasized by Jaffe[11] that such cases should be designated as pseudoaplastic anemia

It is known that there is no essential difference in the bone marrow of the idiopathic and secondary types of aplastic anemia In osteosclerotic anemia the marrow undergoes a change into connective tissue, which later becomes ossified Occasionally the marrow cavity may become obliterated making it impossible to obtain samples of active marrow This may occur in senile osteosclerotic anemia or in Albers Schonberg s marble bone disease

Sternal Marrow in Chronic Myelogenous Leukemia

The characteristic changes in the marrow of a patient with chronic myelogenous leukemia are (1) the presence of an increased number of myeloblasts often exceeding greatly the normal number of 1 to 2 per cent (2) the striking increase in the number of myelocytes of which a large percentage are of the neutrophilic variety although many basophilic and eosinophilic types are present also (3) a definite increase in the cellularity of the marrow there being 75 to 85 cells per high power field present when the leukemic process is fully developed (4) the presence of mitotic figures which are not ordinarily numerous but it is often possible to find them usually in myelocytes or sometimes in myeloblasts after a careful search

Some evidence of the acuteness of the process may be obtained by an estimate of the relative number of myeloblasts and other cells of the granulocyte series which are less differentiated than the myelocytes An increase in the number of these cells is associated with the more acute phases of leukemia

Sternal Marrow in Lymphatic Leukemia

The outstanding feature of the sternal marrow obtained by diagnostic puncture in this form of leukemia is the predominance of lymphocytes It is estimated that usually these cells make up from 40 to 95 per cent of all nucleated cells in the marrow of both the leukemic and subleukemic phases of lymphatic leukemia According to Scott[8] the findings of over 40 per cent of lymphocytes in the marrow suffices for a positive diagnosis but a normal count does not exclude the condition In my opinion it would be more accurate to state that the presence of 40 per cent of lymphocytes in the sternal marrow suggests the diagnosis of lymphatic leukemia but such a finding should not be interpreted to mean that it is incontrovertible evidence of the disease

The examination of the sternal marrow is especially valuable from a diagnostic standpoint in cases of lymphatic leukemia in the subleukemic stage In this phase the marrow is just as characteristic as when the lymphocytes are greatly increased in the peripheral blood One is unable to state from the examination of the marrow alone whether the circulating blood shows characteristic leukemic changes or not

Sternal Marrow in Chronic Monocytic Leukemia (Schilling and Naegeli Types)

In this condition the bone marrow shows characteristic changes which consist of a great increase in the cellularity due to excessive numbers of cells of the

which operate independently, could account for the discrepancies between the findings in the bone marrow and the peripheral blood

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and there is a pale perinuclear zone in some but not all cells Studies with staining methods specific for the plasma cell such as Pappenheim s pyronin methyl green have been said to give unequivocal results[8]

Sternal puncture should be done in all patients in whom the diagnosis of multiple myeloma is suspected If there is no evidence of multiple myeloma cells in the material obtained from sternal puncture then considerable doubt is cast upon the diagnosis although of course this does not exclude the disease

Sternal Marrow in Agnogenic Myeloid Metaplasia of the Spleen

This condition was described first by Henry Jackson Jr and his associates in 1940[1] The clinical picture resembles that of chronic myelogenous leukemia except that roentgen ray does not have a favorable therapeutic effect and the length of life is longer after the onset of symptoms The average duration of life in Jackson s cases was 11 years The hematological picture is similar to that of myelogenous leukemia but it may simulate chronic hemolytic jaundice The bone marrow may appear normal aplastic hyperplastic or fibrotic but it never resembles the picture of leukemia The diagnosis of myeloid metaplasia of the spleen can be made during life by detecting the myeloid cells in the material obtained from splenic puncture along with the evidence secured by sternal puncture indicating that the bone marrow has not undergone the changes of myelogenous leukemia

Sternal Marrow in Infections and Leukemoid Reactions

Our knowledge concerning the changes in the bone marrow in various infections is incomplete and needs additional investigation One desirable reason for increasing our knowledge of these changes is to enable a better differentiation between the bone marrow changes in infection and those in leukemia It is recognized that there is a progressive shift to the left in the granulocytes of the marrow in infections The bone marrow reactions have been divided into four different types in infections by Barta[13] as follows

1 A moderate reaction with an abundance of cells
2 An intense reaction with many promyelocytes or even myeloblasts
3 An extreme reaction with many promyelocytes or even myeloblasts
4 A failure of reaction with a decrease of granular leukocytes

In infections associated with a leukopenia of the peripheral blood as seen in influenza and typhoid fever the findings have been reported as those of a marrow somewhat poor in cells of the granulocyte group especially those which are mature These findings have been interpreted as a maturation arrest

monocyte series In the average case from 65 to 90 per cent of all the cells of the marrow are monocytes promonocytes or monoblasts Often the number of mitotic figures is striking and they even may be seen occasionally in the immature monocytes of the blood Erythropoiesis often is retarded as evidenced by a reduction of all types of normoblasts, especially the basophilic forms

In the Naegeli type of monocytic leukemia the marrow in general may be said to resemble more closely that of chronic myelogenous leukemia In it however are observed a certain number of monocytes, promonocytes and monoblasts The same picture, however occurs in the marrow as in the peripheral blood

Sternal Marrow in Acute Leukemia

This condition may be either an acute exacerbation of chronic leukemia or a primary state Regardless of the variety the changes in the blood and marrow are the same The bone marrow is found to be infiltrated with large numbers of cells of the white blood cell series which are in a primitive state of development It is exceedingly difficult from the changes in the bone marrow, as it is in the peripheral blood to differentiate positively between myeloblasts lymphoblasts and monoblasts Hence from the standpoint of the bone marrow, if one observes that there is a heavy infiltration with cells of the primitive white cell variety, it can be said that an acute leukemia is present but there may be difficulty in determining the type The 3 characteristics of an acute leukemia in the bone marrow are (1) the marrow is filled with immature nongranular cells ( ) the nuclei are large and many contain nucleoli (3) mitotic figures are numerous

Sternal Marrow in Multiple Myeloma

Sternal puncture yields valuable information in patients with multiple myeloma which is either diagnostic or confirms the clinical impression that the patient has the disease In every patient with multiple myeloma whom we have examined during the past 6 years totaling almost 40 cases the sternal marrow has contained the characteristic multiple myeloma cells in every single instance Normally there are about 1 per cent of plasma cells in the sternal marrow whereas in patients with multiple myeloma these cells or very similar ones are found to be increased usually comprising 10 to 15 per cent of all the cells present In some instances they reach a percentage of 50 or more

The so-called multiple myeloma cell which is either a plasma cell or one closely related to it usually is egg shaped and measures from 15 to 30 microns It contains a nucleus which commonly is placed eccentrically The chromatin of the nucleus is stained deeply but the cartwheel arrangement, so characteristic of the normal plasma cell usually is not present The cytoplasm is basophilic

Sternal Marrow in Metastatic Lesions of Bone Marrow

In a certain proportion of cases an experienced observer can detect malignant cells in material aspirated from the sternal marrow in patients who have carcinoma and generalized metastases According to Piney and Hamilton Paterson[14] one is surprised at the frequency with which tumor cells are found in sternal marrow *in the absence of clinical and radiographic signs of metastases* It is possible that the routine use of this procedure might disclose many cases which were thought to be operable but in whom evidence of a spread to the marrow of the sternum indicates that they already had passed through the stage where cure is possible It is the opinion of Piney and Hamilton Paterson[14] that probably the commonest metastatic growths of the bone marrow are secondary deposits arising from carcinoma of the prostate breast stomach kidney and thyroid It should be kept in mind that the recognition of malignant cells requires that one must be an experienced observer and furthermore as only a small sample is examined the absence of malignant cells is of course no proof that the marrow is free from metastases elsewhere

Sternal Marrow in Thrombocytopenic Purpura

In general it may be stated that the bone marrow in this variety of purpura does not show striking changes If there has been extensive bleeding as a result of the reduction in blood platelets the marrow will show the alterations commonly associated with chronic hemorrhage There is one important point for emphasis however and this is the finding in the marrow with reference to the desirability of performing a splenectomy in patients with thrombocytopenic purpura Experience has shown that when splenectomy is successful in alleviating the condition there are megakaryocytes present in the bone marrow This is because the megakaryocytes are present in patients with the primary form of the disease in which splenectomy is successful and are likely to be diminished or absent in those with the secondary form in which the operation is not indicated

Sternal Marrow in Polycythemia Vera

In general it may be said that in patients with polycythemia vera the majority of authors agree that there is a moderate increase in the cellularity of the marrow and that the number of erythroblasts is greater than normal Not only is there evidence of an increased activity of the red blood cells and the white blood cells but for some unknown reason there is also characteristically an increase in the number of megakaryocytes commonly observed

Sternal Marrow in Infectious Mononucleosis

It is important to recognize the alterations which occur in the bone marrow in patients with infectious mononucleosis as the clinical manifestations of the disease may be confused with leukemia In infectious mononucleosis the microscopic appearance of the bone marrow is quite different from leukemia, for it is characterized as hypoplastic but without any radical change from normal The outstanding feature in the average case is the presence of atypical lymphocytes in every field which resembles in all respects the infectious mononucleosis cells' of the peripheral blood It should be kept in mind, however, that these changes are not always present in patients with infectious mononucleosis as the bone marrow in this condition may be entirely normal It is doubtless true that the marrow alterations are dependent to some extent on the stage of the disease in which it is investigated In the early stages of the condition the atypical lymphocytes may not be present either in the circulating blood or the bone marrow

Sternal Marrow in Agranulocytosis

There may be an apparent discrepancy in the marrow changes and the peripheral blood in these patients This is because although the granulocytes in the circulating blood may be greatly diminished or absent the marrow may appear hyperplastic and contain an increased number of granulocytes In some patients the marrow may show an aplasia, but it is now well established that in others there may be evidence of a maturation arrest at the myeloblast stage To me the latter change is the characteristic one of the disease which to the inexperienced might suggest the possibility that the picture in the marrow is one of myelogenous leukemia It is entirely possible that in the future the syndrome of agranulocytosis might be subdivided into several types with different causes and different pathological findings and hence a variable picture in the bone marrow

Sternal Marrow in Gaucher's Disease

The occurrence of anemia leukopenia and thrombopenia in this disease is explained on the basis that there is an infiltration of the bone marrow with foreign cells of the Gaucher type These cells are large, varying from 20 to 40 microns in diameter they are pale and round oval or polygonal in shape One or two oval or round nuclei are present which are relatively small and have a finely granular chromatin structure The nuclei usually are located near the periphery of the cell In some instances the cells may be very large measuring from 70 to 80 microns in diameter and containing 10 to 12 nuclei The diagnosis of this disease is almost always possible by means of sternal puncture

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It should be kept in mind however that in some cases the bone marrow may appear surprisingly normal despite the typical changes in the peripheral blood

Sternal Marrow in Protozoal Diseases

It is pointed out by Piney and Hamilton Paterson[14] that these diseases offer a promising field for study by means of sternal puncture as many of the parasites make their home in the reticuloendothelial system According to these authors sternal puncture not only affords a rapid and safe method of providing material which contains the parasites in large numbers, but also affords an opportunity of studying the mechanisms of the blood changes

Sternal Marrow in Kala Azar

In this condition there is a lymphocytosis monocytosis a hyperplasia of the cells of the reticuloendothelial system and the causative organisms the Leishmania are present in the marrow The parasites are found in the monocytes and also free from cells In some respects they resemble blood platelets but differ from them in having a much complicated structure

Sternal Marrow in Malaria

The marrow in malarial infections is hyperplastic of the normoblastic variety and resembles that seen in other hemolytic anemias In malignant malaria the number of infected corpuscles may be greater in the marrow than in the blood stream It is reported by Piney and Hamilton Paterson[14] that the marrow response which does not disappear for months after recovery from the acute phase of the disease is essentially normocytic and monocytic

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CHAPTER XVII

LEUKEMIA

By RAPHAEL ISAACS

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Definition — Leukemia is a disease of the hematopoietic organs characterized by a progressive block in the maturation of one type of leukocyte There may be a slow or rapid evolution A myelophthisic anemia and a hemorrhagic tendency develop The disease may be associated with a peripheral leukocytosis or a leukopenia at some time during its course Immature forms usually are present in the blood The disease is accompanied by an irregular fever a tendency to relapses and remissions, and there is terminal cachexia

Historical Considerations

The first published note describing in some detail a case of leukemia was that of John Hughes Bennett in the Edinburgh Medical and Surgical Journal October 1, 1845 vol 64 p 413 The patient died and at the autopsy on March 19 1845 four days after death Dr D Craigie who was present recalled having seen a similar case which had been under his care four years previously He published a description of his case in the same number of the Journal

Dr Bennett s description contains many characteristic features of patients with chronic myelogenous leukemia

History John Monteith aged 28 a slater — admitted into the clinical ward of the Royal Infirmary February 27 1845 under the care of Dr Christison He is of dark complexion usually healthy and temperate states that twenty months ago he was affected with great listlessness on exertion which has continued to this time In June last he noticed a tumor in the left side of the abdomen which gradually increased in size till four months since when it became stationary It was never painful till last week after the application of three blisters to it since then several other small tumors have appeared in his neck axillae and groins at first attended with a sharp pain which has now however disappeared from all of them Before he noticed the tumor he had frequently vomiting in the morning The bowels are usually constipated appetite good is not subject to indigestion has had no vomiting since he noticed the tumor he has used chiefly purgative medicines especially croton oil employed friction with a liniment and had the tumor blistered

Symptoms on Admission On admission there is a large tumor extending

the gelatinous appearance of a healthy decolori ed clot When squeezed out of the veins as was sometimes accidentally done where they were divided it resembled thick creamy pus In some portions of the veins the clot was wholly formed of red coagulum In others it was divided into red and yellow In a few places the yellow formed only a streak or superficial layer upon the red or covered the latter with spots of various sizes Whether this coagulum existed in all the veins could only have been ascertained by a complete dissection of the body It was seen however that the femoral veins after passing under Poupart s ligament were empty and perfectly healthy as far down as the Sartorius muscle The external and internal iliac veins, as well as the pelvic veins were full and distended The azygos both axillary and jugular veins were full also the longi tudinal, the lateral and other sinuses at the base of the cranium and veins rami fying on the surface of the brain In this last situation some of the veins ap peared as if full of pus whilst others were gorged with a dark coagulum In the aorta and external arteries were a few small clots resembling those found in the veins These vessels however were comparatively empty The basilar artery at the base of the brain was distended with a yellow clot

Vessels The arteries and veins themselves were perfectly healthy Al though carefully looked for in no place could thickening or increased vascularity be observed Nowhere was the clot adherent to the vessels but on the con trary it readily slipped out when an accidental puncture was made in them

* * * * * * * *

Abdomen On the inferior surface of the diaphragm there existed a firm almost cartilaginous deposit about a line in thickness of a white color oval form, two inches long by one and a half broad with irregular margins which were com posed of several rounded tubercular bodies the size of a small pea and of a fibrous structure The liver enormously enlarged from simple hypertrophy Its structure throughout healthy Gall bladder enlarged and distended with a clear pale yellow bile The whole weighed ten pounds twelve ounces The pleen also enormously enlarged from simple hypertrophy It was of a spindle hape largest in the centre tapering towards the extremities It weighed seven pounds twelve ounces It measured in length fourteen inches in breadth at its widest part seven inches and in thickness four and a half inches Towards its an terior surface was a yellow firm exudation about an inch deep and three inches long The peritoneum also covering a portion of its anterior surface was thick ened opaque and dense over a space about the size of the hand Both kidneys healthy The stomach and intestines healthy throughout About four inches from the anus the superior haemorrhoidal veins were distended on both sides external to the rectum They formed two chains of tumors about three inches

from the ribs to the groin and from the spinal column to the umbilicus, lying on the left side It is painful on pressure near its upper part only Percussion is dull over the tumor pulse 90 states that for three months past he has not lost in strength There is slight oedema of the legs *To have two pills of iodide of iron morning and evening*

"*Progress of the Case* March 1st — Urine of yesterday somewhat turbid when just passed natural in color, acid to litmus sp gr 1 013 Sediment presents cubic crystals under the microscope disappears almost entirely on the addition of aqua potassae but is unaffected by nitric acid The filtered urine is not affected by aqua potassae and yields only a slight white haze when boiled March 9th — Oedema of legs increased They have been bandaged with flannel rollers ℞ Potassae Carbonatis dr i Spiritus Aetheris Nitrici dr iv Aquae Menthae oz iij Aquae fontis oz ij M Sumat unciam ter in die March 10th — Tormina and considerable diarrhoea urine not increased Habeat haustum Olei Ricini oz ss statim et exactis quatuor horis Opii gr ii March 13th — Attacked this morning with heat of skin thirst pulse 110, full very compressible The diarrhoea which had been checked, returned yesterday none this morning after taking an opium pill Urine 100 ounces Omittantur medicamenta Sumat statim Pulveris Ipecacuanhae et Opii gr x, et repetatur dosis singulis semihoris ad tertiam vicem March 14th — No sweating from the powders diarrhoea still rather troublesome pulse 100 softer tongue dry and brown, febrile expression of countenance resembling that of typhus ℞ Aquae Acetatis Ammoniae dr vi Solutionis Morphiae dr i Aquae fontis oz iij Syrupi oz j Sumat unciam quarta quaque hora Habeat decoctum hordei pro potu March 15th — Died suddenly in the morning

'*Sectio Cadaveris* March 19th (four days after death)

'Externally the body presented a considerable prominence of the ensiform cartilage and false ribs on both sides The abdomen was contracted considerable dulness on percussion on left side which had previously been marked out by a line formed with nitrate of silver No ascites or oedema of the limbs

Blood The blood throughout the body was much changed In the right cavities of the heart pulmonary artery venae cavae, vena azygos external and internal iliac veins, and many of the smaller veins leading into them it was firmly coagulated, and formed a mould of their size and form internally In the cavities of the heart and venae cavae the blood when removed was seen to have separated into a red or inferior and a yellow or superior portion The red portion was of a brick red color it did not present the dark purple smooth and glossy appearance of a healthy coagulum, but was dull and somewhat granular on section, and when squeezed readily broke down into a grumous pulp The yellow portion was of a light yellow color opaque and dull, in no way resembling

pressed exuded a fluid that was crowded with corpuscles some resembling the colorless corpuscles already alluded to others oval and round containing a distinct nucleus

The ultimate textures of the muscles brain nerves etc were carefully examined and found normal

Six weeks after the articles of Bennett and of Craigie appeared a third report by Prof Virchow was published in Froriep s Notizen Number 780 November 1845 Bennett describing the abnormal corpuscles in the blood as identical with those of pus called the disease leucocythemia (white blood cell blood) Virchow used the term leukhemia (white blood) and developed the concept that the cells were white blood cells rather than pus Neumann[1] described the changes in the bone marrow accompanying the disease Three types of leukemia were distinguished splenic lymphatic and myelogenous Ehrlich showed the identity of the plenic and myelogenous forms (splenomyelogenous leukemia) Friedrich[3] described a case of acute leukemia and Ebstein later formulated the type as a clinical entity More recently monocytic leukemia has been recognized as separate from the chronic myelogenous type

The first use of x ray therapy in the treatment of the disease was in 1902 by W A Pusey[5], reported by Nicholas Senn

Details of the history of leukemia may be found in Rolleston s History of Haematology (pp 1171–1173) in John Hughes Bennett s Clinical Lectures on the Principles and Practice of Medicine (3rd ed 1866 pp 867–900) and in H Hirschfeld s Leukamie und Verwandte Zustande in Enzyklopedia der klinischen Medicin Spezieller Teil Handbuch der Krankheiten des Blutes und der Blut bildenden Organe bd 1 pp 11–218 by A Schittenhelm Julius Springer Berlin 1925

Types of Leukemia Nomenclature

Many names have accumulated in the literature Those who feel that leukemia is a neoplastic process use such terms as leukemic lymphoblastoma leukemic myeloblastoma or monoblastoma The names myeloid or lymphoid leukemia suggest that it is felt the cells resemble but are not identical with those of the marrow or lymph nodes The terms myelogenous or lymphogenous suggest the point of origin of the leukemic process in the patients whereas myelocytic lymphocytic or monocytic suggest the cell type involved An older term now seldom used was polycythemia vera alba expressive of the forms with leukocytosis Other terms are leukocythemic or leukemic as contrasted with aleukocythemic aleukemic subleukemic or leukopenic

The types of leukemia which are most common are chronic and acute myelogenous leukemia chronic and acute lymphatic leukemia chronic and acute mono

long consisting on the one side of three swellings as large as a walnut on the other of one swelling somewhat larger They were filled with a red coagulum, broken down into a grumous mass The lymphatic glands were everywhere much enlarged In the groin they formed a large cluster, some being nearly the size of a small hen s egg and several being that of a walnut The axillary glands were similarly affected The bronchial glands were not only enlarged, but of a dark purple color and in some places black from pigmentary deposit The mesenteric glands were of a whitish color some as large as an almond nut A cluster of these surrounded and pressed upon the ductus communis choledochus The lumbar glands were of a greenish yellow color also enlarged forming a chain on each side and in front of the abdominal aorta, more especially at its bifurcation into the iliacs

" No collection of pus could be found in any of the tissues

Microscopic Examination The yellow coagulum of the blood was composed of coagulated fibrin in filaments intermixed with numerous colorless corpuscles which could be readily squeezed out from it when pressed between glasses Where the yellow coagulum was unusually soft the corpuscles were more numerous and the fibrin was broken down into a difiluent mass, partly molecular and granular partly composed of the debris of the filaments broken into pieces of various lengths The corpuscles varied in size from the 80th to the 120th of a millimetre in diameter they were round their cell wall granular and presented all the appearance of pus corpuscles Water caused them to swell and lose their granular appearance and acetic acid dissolved the cell wall and caused a distinct nucleus to appear This nucleus was composed sometimes of one large granule about the 200th of a millimetre in diameter at others of two or three smaller granules as is seen in corpuscles of laudable purulent matter The red portion of the coagulum contained a smaller number of these colorless corpuscles mixed with a multitude of normal yellow corpuscles The colorless corpuscles now described were found in the blood throughout the system They were seen in the veins and arteries ramifying on the brain in the coronary veins hemorrhoidal tumors and wherever the blood was examined On stripping off a portion of the pia mater and examining the capillary vessels of that membrane all that were not too minute to contain them *were found crowded with the same corpuscles* This fact was confirmed by Dr Allen Thomson, to whom I sent a portion of the brain for that purpose

The cartilaginous deposit on the inferior surface of the diaphragm was composed of dense fibrous tissue in which numerous granules and molecules were observed The exudation in the spleen was composed of amorphous fibrin mixed with numerous molecules granular and imperfect cells These were intermingled with bundles of filamentous tissue The enlarged lumbar glands on being

TABLE I

Age Groups	1921–1925		1933–1937	
	Male	Female	Male	Female
1–14	1 5	0 8	2 7	2 2
15–24	0 9	0 7	1 6	1 0
25–34	1 2	0 8	1 3	1 4
35–44	1 3	1 2	2 3	2 3
45–54	2 4	1 8	3 4	3 5
55–64	3 9	2 4	7 1	5 1
65–74	4 2	1 8	10 1	7 1

In the years 1921–1937 the annual standardized death rates per 100 000 white persons ages 1 to 74 were as shown in Table II

TABLE II

Year	Male	Female
1921	1 6	1 0
1922	1 7	1 1
1923	1 4	0 9
1924	1 8	1 1
1925	1 8	1 2
1926	1 4	1 4
1927	1 9	1 7
1928	1 5	1 6
1929	2 0	1 9
1930	2 1	1 8
1931	2 6	1 9
1932	2 5	2 1
1933	2 4	2 0
1934	2 6	2 5
1935	3 4	2 7
1936	2 8	2 2
1937	2 9	2 5

The total number of deaths in the United States in which leukemia was given as the cause was in 1936 3 628 2 086 males 1 542 females For the period 1934–1936 there were 10 094 deaths 5 762 males 4 332 females in the white population with an average of 3 528 per year The age distribution is shown in Table III

cytic leukemia The names are not ideal or comparable, but history and usage have crystallized these forms Nothing can be gained by frequently changing them

Rarer forms are plasma cell, eosinophile, basophile, lymphosarcoma cell megakaryocyte leukemia and other types in which tissue cells appear in the blood stream secondary to hyperactive proliferation in the body Some are extremely difficult to classify as the cell types are atypical

When the cells become extremely immature, the terms stem cell leukemia myeloblastic lymphoblastic, monoblastic, primitive cell or blast leukemia are used This stage may be reached within six weeks, acute leukemia, or it may be the terminal stage of chronic leukemia An intermediate stage, subacute, sometimes is noted

In some individuals the leukemic process is confined mostly to the blood forming organs with a normal or decreased number of cells in the peripheral blood stream aleukemic leukemia, whereas in others a flooding of the peripheral blood with immature forms results in leukocytosis

Occurrence and Distribution

Leukemia has been described in practically all parts of the world both in man and animals It affects men dogs pigs, sheep cattle, fowl, mice cats, monkeys horses guinea pigs[6] The manifestations in different animals vary and it is possible that the leukemic picture results from varying causes

In the Metropolitan Life Insurance Company s statistics for 1921 to 1935 out of a total of 4,333 deaths from leukemia there were 3 990 white people and 343 colored people In the total population the incidence in white males was 2 0 and in white females 1 7 per 100 000 population, whereas the incidence in the colored population in males was 1 3 and in females 1 1 In the Johns Hopkins Hospital statistics Wintrobe[7] the incidence in white patients was at least twice that in colored individuals In a hospital population of 324 785 Jackson[8] reported 333 cases In 8 693 autopsies there were 78 cases of leukemia

Age and Sex Incidence

Leukemia may appear in individuals from birth to old age In the young the course more frequently is acute whereas in the older individuals the course usually is chronic although acute types may be noted at almost any age period

The average annual death rate for leukemia of all types per 100 000 white persons in the Metropolitan Life Insurance Company s statistics is shown in Table I

cytic leukemia making the numbers slightly different from the most modern figures

Heredity

Quite a number of case reports have appeared in which more than one patient with leukemia appeared in closely related individuals However this occurrence is rare enough to make heredity of leukemia in human beings quite unlikely In mice which are 100 per cent susceptible to the disease strains can be developed but some feel that this is not true inheritance of the disease However in some groups of mice and fowls the transmission follows the rules of heredity Leukemia in these animals however is not strictly comparable to the human form of the disease

Leukemia may appear in families in which other members had unusual disease of the blood forming organs such as pernicious anemia aplastic anemia and other types of leukemia and lymphoma

Theories as to Etiology

The cause of leukemia in man is not known Among the theories of the etiology are (a) neoplastic theory a type of cancer (b) a response to infection (c) a deficiency disease loss of control of hematopoietic function

Neoplastic Theory

The uncontrolled production of leukocytes especially in the blast stage i e the acute or the terminal stage of the disease resembles other forms of cancer The response to x ray therapy is similar in both diseases when the leukemic cells are fairly mature but not when the cells are all blasts Neoplasms of other types may exist in the same patient along with leukemia In some patients with neoplasms some of the neoplastic cells may appear in the blood stream

Human leukem a cannot be transmitted by transfusion of leukemic blood but fowl leukemia may be tran mitted to fowls by cell free extracts and mouse leukemia to other mice by cell transplantation Leukemia may be produced in susceptible animals by the same agencies as used in the production of cancer Leukemia has followed the injection of benzol indol tar and sodium 1 2 5 6-dibenzanthracene 9 10-endo alpha beta succinate A marked increase of leukemia in susceptible mice has followed the exposure to small doses of x ray Isolated cases of leukemia in man have been reported after exposure to various chemicals but the relationship is not necessarily causative

A number of examples of leukemia have been reported in individuals exposed

TABLE III

Age Groups	Males		Females	
	Total	Per 100 000	Total	Per 100 000
Under 1 yr	112		85	
1–14	1110	2 5	764	1 8
15–24	469	1 5	317	1 0
25–34	421	1 6	357	1 3
35–44	597	2 5	520	2 2
45–54	796	3 9	685	3 6
55–64	1073	7 8	780	6 0
65–74	882	11 8	616	8 3
75–84	280	10 5	195	7 0
85–94	26	7 8	13	3 1
95 and over	1	14 8		

Statistics for the year 1939 for the older groups 65 years and over, for the United States are as follows total deaths 966 or 11 0 per 100 000 population 65–69 years 363 deaths or 9 8 per 100 000 population 70–74 years 290 deaths or 11 6 per 100 000 population 75 and over 313 deaths or 12 3 per 100,000 population In the period from 1921 to 1935 there were 1 897 deaths of white men 2 093 of white women 170 of colored men 173 of colored women

From data published from various parts of the world the sex incidence in chronic myelogenous leukemia is about 3 male to females in chronic lymphatic leukemia 3 to 1 in chronic monocytic leukemia 2 to 1 and in acute leukemia 5 to 1 In chronic lymphatic leukemia the incidence in females is higher below the age of 15 years and in the decade between 40 to 50 years Acute lymphatic leukemia is relatively more frequent in females during the first year of life than in subsequent years while after the age of 15 the incidence is about 65 per cent males to 35 per cent females

The age incidence for the various types of leukemia shows a different distribution for each group In acute leukemia of all types the majority of the cases occurred before the 35th year in some groups before the 5th year In chronic myelogenous leukemia most cases appear in the 30 to 40 year period with fewer cases in the younger and older groups In chronic lymphatic leukemia most cases appear during the 45 to 55 year period In chronic monocytic leukemia the 55 to 65 year group contains the most cases In the cases reported in the literature most of the cases of monocytic leukemia living less than three months came in the 30 to 40 year group[91] While the majority distribution of the age incidence is as just given cases of all types have been reported from infancy to old age In the earlier published statistics myelogenous leukemia included mono

losis have been found in patients with lymphatic leukemia Pernicious anemia like syndromes may terminate in myelogenous leukemia[15] in monocytic leukemia or be associated with lymphatic leukemia[16]

Polycythemia vera may terminate in a myelogenous leukemia picture especially after x ray therapy has been used The picture generally is marked by an unusual number of nucleated red blood cells The syndrome in which there is both polycythemia and a leukemic blood picture is characterized as *erythro leukemia*[1]

The term leukanemia formerly was used to describe the association of a blood picture like that of pernicious anemia with that of leukemia

Symptomatology and Pathological Changes

General

The chronic forms of leukemia have many symptoms in common The first feature in most individuals is ease of fatigue In studying the histories in retrospect this symptom appeared in many cases years before the true diagnosis became evident Another early symptom not diagnostic at the time is ease of bruising Purpuric areas appear with little or no known trauma Late in the disease a tendency to purpura and to hemorrhages from nose gums gastro intestinal tract genitourinary system skin serous surfaces internal organs eyes or ears may be very marked and may dominate the terminal picture

The symptomatology of leukemia is secondary to several etiological factors

1 Associated with an elevated basal metabolic rate are irritability insomnia nervousness abnormal perspiration loss of weight tolerance to cold and a rapid pulse rate

2 The enlarged organs metastatic nodules or masses of lymph nodes may give rise to tumors or to pressure symptoms such as pain cough dyspnea diarrhea constipation feeling of fulness in the abdomen frequency of urination nausea dizziness headache and other neurological symptoms herpes and through the mechanism of referred pain tenderness in the shoulder over the sternum and pain in the shoulders especially the left

3 In proportion to myocardial insufficiency especially when associated with anemia there is dyspnea edema ease of fatigue headache giddiness nausea vomiting weakness and loss of appetite

4 Associated with the leukemic changes there is evidence of abnormal metabolism producing cachexia headache joint pains and fever

5 Many symptoms arise from the hemorrhagic tendency or from the anemia

6 Terminally there may be toxic symptoms secondary to infection

to much x ray or radioactive substances While it is definite that this type of irradiation has a profound effect on the marrow, there must be a constitutional factor in the patient, which determines the leukemic course of the disease rather than aplastic anemia, skin cancer or other manifestation

In mice, not usually susceptible to leukemia, feeding milk from susceptible mice did not increase the incidence of leukemia, as it does with cancer[11] It has not been possible to produce leukemia in man or animals by trauma Trauma may call attention to an existing leukemia or may aggravate a slow growing or latent type However, the discrepancy between the incidence of trauma in human beings and of leukemia is so marked that the association is considered fortuitous

Infection Theory

Some infections are associated with a polymorphonuclear leukocytosis others with lymphocytosis or monocytosis Leukemia commences with a rapid production of mature cells then the degree of maturation decreases until eventually the cells do not progress beyond the blast stage A somewhat similar picture, a leukemoid condition may follow severe infection and disappear with recovery The fever accompanying leukemia suggests a type of infection, although fever is not uncommon in patients with cancer

No definite data have been accumulated as to the type of infection that this may be nor have any organisms been isolated with which the disease can be reproduced Babies of leukemic mothers do not have leukemia, suggesting that the etiological factor does not pass through the placenta

Deficiency Disease Theory

The uncontrolled growth of the cells in leukemia suggests the possibility that some normal controlling factor is deficient or the over production of a stimulating factor So far no food or tissue factor has been discovered which has this stimulating effect Certain infections produce leukocytosis, often extreme and the presence of a leukocyte stimulating factor is postulated The work of Wearn Miller Heinle and others[1, 1, 14] suggests that there is a substance in the urine of patients with chronic myelogenous leukemia, which stimulates myeloid hyperplasia and metaplasia, when injected into guinea pigs

INTERRELATIONSHIP OF LEUKEMIA AND OTHER DISEASES

Syphilis is not a cause of leukemia although a few cases of syphilis have been reported with a leukemoid blood picture Lymphatic leukemia has been associated with diabetes in a number of patients Malaria as well as tubercu

Most patients with leukemia experience some eye symptoms during the cour e of the disease The retinal hemorrhages are not necessarily a bad prognostic sign and in the absence of complications or further hemorrhages usually give no symptoms after about five days

Lacrimal and Salivary Glands

A few patients develop a bilateral enlargement of the lacrimal and salivary glands associated with leukemic infiltration so-called Mikulicz syndrome There is usually no pain or inflammatory reaction and no other symptomatology than the hard masses [1] [3]

Lymph Nodes

The lymph nodes become greatly enlarged in lymphatic leukemia less fre quently in myelogenous and monocytic leukemia Rarely they are of normal size in lymphatic leukemia The lymph nodes in lymphatic leukemia are fairly firm but soft and they remain discrete They are not tender In lympho sarcoma a neoplastic type of cell invades the capsule and binds the nodes to the surrounding tissue In tuberculosis and inflammatory lesions perinodular in flammation causes adhesions In infectious mononucleosis the nodes usually are tender at some stage as they are in inflammatory le ions

Myeloid invasion or metaplasia may be noted in the nodes in myelogenous leukemia In lymphatic leukemia an increase in the number of lymphoid cell destroys the normal architecture of the nodes and there is no follicular hyper trophy as in giant follicular hyperplasia The germinal centers are lost and the mass becomes homogeneous In the chronic cases the cells are mostly small and medium sized lymphocytes with numerous mitoses In acute leukemias the predominant cell is the stem cell or blast

The tonsils are seldom involved in chronic leukemia but may be markedly hypertrophied inflamed and necrotic in acute leukemia Surface hemorrhages however may appear in any type

The appendix Peyer s patches and gastrointestinal lymph nodules may be involved to different extents in different individuals There is but little corre lation between the size of the lymph nodes and the peripheral blood picture This is e pecially true in the aleukemic forms

Spleen

In lymphatic leukemia there may be hypertrophy of the splenic tissue cells or invasion with lymphocytes with obliteration of the normal architectural struc

Very few of the symptoms except cough, priapism and thrombosis appear to be related directly to the elevated leukocyte count, although there is usually a general alleviation of abnormalities when the white blood cell count is reduced to a normal range The same symptoms may be present when the peripheral leukocyte count is high or low as in aleukemic forms

In the absence of a characteristic blood picture Baldridge and Fowler[18] suggest the following criteria which would make one suspect leukemia (1) severe unexplained anemia with a color index of about 1 and with a moderate increase in reticulocytes, ( ) hemorrhagic purpura which does not respond to transfusions of blood (3) tumefaction of the gums (4) unexplained enlargement of the spleen or lymph nodes (5) symptoms of arthritis without selective atrophy of the muscles, increased tendon reflexes or palpable changes in the joints (6) painful nerve roots or deep bony pain (7) lytic lesions in bones e g lesions of the ribs seen in a roentgenogram of the chest, (8) leukopenia with a shift to the left in an afebrile patient, (9) erythroblasts found unexpectedly in a smear (10) pathological fractures, (11) high consumption of oxygen in a patient without fever or exophthalmic goiter, (12) unexpected acute enlargement of the breasts or ovaries

Less important suggestive diagnostic criteria are (1) reddish gray, non liquefied tissue discovered at operation for osteomyelitis (2) priapism (3) abnormally high value for plasma globulin or fibrinogen (4) unexplained hypercalcemia or hypocholesteremia (5) Bence Jones proteinuria, (6) abnormally rapid rouleau formation (7) unexplained anticomplementary Wassermann tests

To these may be added unexplained fever elevated blood uric acid, unexplained ease of fatigue abnormal perspiration and loss of weight

With these suggestive symptoms and signs the actual diagnosis can be made by a study of the blood or of tissue obtained by sternal puncture

Eye

At any time the patient may note a blurring of vision in one or both eyes Examination of the retina shows peripheral reddening and punctate hemorrhages which develop into areas with white centers from infiltration with leukocytes In some there is engorgement of the retinal veins or arteries The disc margins may be clear or blurred There may be nodular or linear collections of leukemic cells[19] the latter appearance is caused by cells in the sheaths of vessels

In a few patients leukemic nodules in or around the orbit may cause visible tumors and exophthalmos as in chloroma The conjunctiva becomes edematous and extruded and secondary infection may develop The pus is rich in polymorphonuclear neutrophiles even in lymphatic leukemia

Among the symptoms which may be noted are cranial nerve palsies anesthesia loss of reflexes signs of pyramidal tract disease paresthesias herpes meningeal disease symptoms headache coma paralysis tremors numbness and tingling of the fingers The symptoms depend on the nerves involved and have a widespread distribution

Some of the symptoms are the result of pressure or infiltration of tissues with leukemic cells but some no doubt are secondary to treatment with x ray or arsenic There may be considerable relief however after adequate x ray therapy especially marked in herpes

The cerebrospinal fluid may be under increased pressure with increased amounts of protein The cell count in it may be within normal limits or be very high and immature forms characteristic of the type of leukemia involved are present The sugar content has been normal in the cases studied

Gastrointestinal Tract

The gastrointestinal tract may be involved by pressure of enlarged organs or lymph nodes by diffuse or nodular infiltration by involvement of the intrinsic lymphoid nodules by hemorrhage and by referred neurogenic processes to cause symptoms

In one series of cases achlorhydria after histamine injection was found in 13 per cent of the patients with chronic myelogenous leukemia in 53 per cent of those with chronic lymphatic leukemia in 33 per cent of those with aleukemic leuk mia and in 2 of 5 patients with acute leukemia Because of the age of the patients achlorhydria being more common in older individuals these observations may be considered as significant only in the chronic lymphatic group

There may be no gastrointestinal symptoms in many patients At some time in the disease there is usually nau ea in addition to that produced by x ray therapy Vomiting is not common Diarrhea may follow arsenic treatment or it may be associated with defective fat absorption because of enlarged intestinal and mesenteric lymph nodes Constipation is a marked feature and sometimes is related to mechanical pressure At other times it is related to a defective intake of food from anorexia or a feeling of fulness when food is taken into the compressed stomach

Gastric ulcers may be present with or without symptoms and may be discovered only at autopsy They are discrete punched out areas with leukemic infiltration of the surrounding ridge

The gastrointestinal mucosa may show local or generalized thickening In lymphatic leukemia the lymphoid nodules throughout the tract may be hyper

ture In myelogenous leukemia there is first infiltration with bone marrow cells later myeloid metaplasia As a rule the spleen enlarges early in the disease, and whenever there is an exacerbation an increase in size is noted The enlargement is due partly to growth of cells and partly to the storage or filtering out from the blood stream of leukemic cells In chronic myelogenous leukemia the average size of the spleen in a group of cases was 1879 2 grams and in chronic lymphatic leukemia 1 97 5 grams In this series of Krumbhaar [1] spleens weighing 4 930 and 5 380 grams were found in chronic myelogenous leukemia, and in chronic lymphatic leukemia one weighing 4 400 grams

There may be hemorrhages followed by fibrosis or infarcts and the capsule *may be greatly thickened Adhesions to the diaphragm and surrounding organs* may form

In the spleen and lymph nodes of chronic myelogenous leukemia there may be myeloid metaplasia or transformation or the tissue may be displaced by rapidly growing lymphocytes or blasts After x ray or radium therapy there is a short period of more rapid growth, followed by a period of decreased cellular multiplication In heavily irradiated nodes there may be fibrosis and often an increase in the number of eosinophile cells

Liver

The liver usually is enlarged in leukemia and shows characteristic distribution patterns of the leukemic infiltrations In the myelogenous and monocytic types there is accumulation of myeloid cells in the sinusoids At times nodules *of myeloid tissue displace the liver cells myeloid metaplasia* It is important to note that the degree of myeloid metaplasia is variable and is absent in some cases, especially in the aleukemic types

In lymphatic leukemia nodules or accumulations of lymphoid tissue surround the branches of the portal vein periportal and perivascular infiltration The blood vessels and capillary channels may be engorged with leukemic cells

Areas of atrophy of the liver cells may be found but jaundice from this source is unusual in leukemia If present usually it is associated with obstruction of the bile passages by nodular growths

Nervous System

In leukemia the central and peripheral nervous systems are involved in several ways There may be diffuse perivascular infiltration focal infiltration nodular tumor masses hemorrhage localized degenerative changes congestion and leukemic polyneuritis from infiltration of peripheral nerves

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the terminal stages It is not uncommon in acute leukemia The blood may be from one or both kidneys but may arise also from the bladder wall The bladder may be edematous and congested and leukemic infiltrations may appear in the walls Renal hemorrhage if accompanied by local or generalized hydronephrosis may be associated with pain in the lumbar region

Infiltrations in the prostate may give rise to signs of obstruction and all the symptoms of prostatic hypertrophy These are relieved by x ray therapy

Priapism from leukocytic congestion and thrombosis in the corpus cavernosa is a rare but frequently mentioned symptom In about ooo cases of all types of leukemia we have encountered it definitely in only two although other patients may not have admitted it It has been reported as involving the clitoris It is reported as occurring less often in lymphatic than in myelogenous leukemia The duration may be from days to months accompanied by severe pain and difficulty of urination

Usually there is disturbance in menstruation In some it stops In others it is so profuse as to exsanguinate the patient This is especially true in the acute cases and in the terminal stage blast stage of the chronic forms

Pregnancy may run a normal course and the infant be normal There may be severe crowding of the abdominal viscera between the enlarged spleen and uterus The baby never is leukemic As a rule pregnancy does not influence the immediate course of the leukemic process unless there is induced or surgical abortion In acute leukemia this is followed quickly by death In chronic leukemia there may be no apparent ill effects or the patient may die soon after No clinical reports of bleeding to death have been encountered In x ray treatment of pregnant women there is always danger of the production of an abnormal child If arsenic administration is effective it is the method of choice for treatment during pregnancy

Most of the cases of pregnancy in leukemia that have been reported were in the acute or chronic myelogenous form A few cases of pregnancy in acute lymphatic leukemia have been recorded In lymphatic leukemia infiltration of the uterine mucosa may be marked and deter pregnancy[3]

Heart

The heart may be fairly normal in function throughout much of the disease but with the anemia and fever tachycardia hemic systolic murmurs myocardial anoxemia and myocardial insufficiency develop The apex because of the enlarged spleen becomes elevated and appears in the anterior axillary line This makes it difficult to evaluate the heart measurements and may give shift in electrocardiographic tracings with the false impression of left ventricular preponderance

trophied and transformed by the leukemic cellular growth Intussusception has been noted associated with localized leukemic infiltration

Cases showing extensive lymphoid hyperplasia without other symptoms of leukemia have been described as pseudoleukemia gastrointestinalis[30,31,3,33]

Hemorrhage may be of the capillary, oozing type, at other times erosions lead to bleeding from larger vessels The bleeding tendency is severe in acute leukemia in advancing lymphatic leukemia and in the terminal stages of chronic leukemia There may be bleeding from the gums or submucous hemorrhages along the entire tract with vomiting of blood or blood in the stools

Lungs and Mediastinum

Involvement of the lungs usually takes the form of congestion with infiltration of the leukocytes in the perivascular spaces Metastatic foci develop with the formation of bone marrow or lymphoid cells The hilar nodes frequently are enlarged and this is especially marked in lymphatic leukemia Pressure gives rise to a paroxysmal non productive cough which does not respond to ordinary sedatives or cough medicines Capillary congestion with large leukemia cells reduces the area of circulation and may be a source of coughing

The hilar and mediastinal nodes swell after x ray irradiation and then decrease rapidly in size They may erode into a bronchus or the trachea The swelling after irradiation may make the symptoms more marked during the first twenty four hours after treatment and the dyspnea may require oxygen inhalation or surgical intervention in exceptional cases

Thymus

The thymus rarely is involved in the hyperplastic growths of leukemia There may be invasion with leukocytes but more often the organ appears atrophic the process being accelerated at times by irradiation therapy Malignant thymoma rarely may be accompanied by a leukemic blood picture The thymus cells in the blood stream resemble small lymphocytes but are distinctly smaller The nuclei are round and less than 7 5 microns in diameter

Genitourinary Organs

Infiltration of the kidney may be diffuse or nodular Occasionally visible, marble like nodules are manifest on cross section Albuminuria appears in from 15 to 20 per cent of the patients with chronic leukemia and is more marked in

1 There is a more or less generalized dissemination of cutaneous and subcutaneous nodules These may coalesce and form large plaques Clinically the disease in this form may resemble mycosis fungoides or Boeck s sarcoid

The maculopapular type of eruption may simulate a secondary syphiloderm or erythema multiforme

3 The deeper lesions which involve the corium and subcutaneous tissue are nodular or tumorous and must be distinguished from Kaposi s sarcoma

4 The individual lesions pass through a cycle of development and of involution and changes often can be detected from day to day In their evolution they increase in size and change in color from red to bluish red During involution they become dusky and fade finally disappearing entirely or leaving gray or pale yellowish red macular areas

5 The lesions sometimes undergo central softening and necrosis and then slough leaving a crater like ulceration Occasionally the lesions may become bullous or purulent owing to superimposed infection

6 The nodules may occur in localized groups but a generalized dissemination is more frequent The pattern is usually asymmetrical and all parts of the body are involved

7 The cutaneous lesions may be the first objective sign of the disease and they may precede or follow the characteristic hematological findings The cutaneous changes are not pathognomonic of monocytic leukemia and the diagnosis of this type of leukemia must be established by examination of the blood together with biopsy studies of the lesions

8 Roentgen treatment may result in a regression of the lesions which occasionally is striking but this effect is only temporary

The specific infiltrative cells are oxidase negative in lymphatic leukemia but usually are oxidase positive in the myelogenous and monocytic forms

The generalized nodular lesions in leukemia frequently are of bad prognostic significance and death may occur in a few weeks or within four months

Bones and Joints

The bone lesions may be noted by x ray or there may be palpable masses or pain may be the outstanding feature Pathological fracture may call attention to the lesion

In x ray films there may be rarefied areas in the medulla and cortex of the long bones with elevation of the periosteum with a very fine lace work of new bone on the outside The skull and pelvis may show fine mottling In children there may be a narrow zone of diminished density proximal to the metaphysis of the long bones with generalized osteoporosis or slight elevation of the perios

With myocardial insufficiency signs of congestion in the lungs and liver appear and there is edema of the lower extremities there is dyspnea on slight exertion The liver frequently already enlarged becomes tender

At autopsy diffuse rarely nodular infiltration of the myocardium is found with evidences of myocardial degeneration There may be an increased amount of pericardial fluid blood tinged at times The pericardium as well as the serous surfaces of other organs may be covered with petechial hemorrhages, and they are present also in the myocardium

Skin

Skin changes are encountered frequently in patients with leukemia There may be petechial hemorrhages or large bruise marks which appear on any part of the body Occasionally vesicles or blebs may appear, and a hematoma may form Leukemic infiltrations may cause indurated nodules in the skin In the center of some of the large nodules umbilication may appear, sometimes necrosis The lesions have been grouped as leukemids, non specific lesions and leukemic lesions aggregations of leukemic cells Of the former group purpura herpes[13] and prurigo lymphatica i e thickening of the skin with chronic inflammatory changes and itching are examples The true leukemia cutis occurs in all types of leukemia The nodules often reddish or bluish in color, vary in size from one to fifteen millimeters and may be isolated or widely distributed There is infiltration of areas in the corium and the upper layers of the subcutaneous tissue The cells are the characteristic leukemic cells of the disease often in a grossly *immature stage*[3]

In lymphatic leukemia there may be a progressive reddening of the skin erythrodermia, with mild desquamation and generalized enlargement of the lymph nodes There is infiltration of the upper layers of the skin with dilatation of the blood vessels Loss of heat gives rise to chilly sensations and there may be pruritus Another type of lesion is universal leukemia of the skin, in which there is a rather widespread infiltration of the skin with lymphoid cells Mycosis fungoides may be associated with a lymphatic leukemic blood picture

Many types of skin lesions occur in monocytic leukemia[3, 9] There are purpuric necrotic pustular and bullous lesions urticaria or pigmentation in addition to nodular infiltrations Macules and papules, resembling a secondary syphilid and developing a slate blue color and nodules palpable deep in the corium form two of the indurative types Exfoliative dermatitis has developed in patients with lymphatic and with monocytic leukemia[10]

Freeman and Koletsky[41] summarize the characteristics of the cutaneous lesions in monocytic leukemia as follows

increase of organic phosphorus in the plasma these values returning to normal as the patient is benefited and as the leukocytes approach normal values in the blood

6 No variations of inorganic phosphorus occur in the plasma or cells before during or following treatment with roentgen rays

7 The glutathione content of the blood is elevated in leukemia

8 There is a tendency at least in myelogenous leukemia in relapse for the total proteins of the blood plasma to be decreased together with a tendency for reversal of the albumin globulin ratio

9 Cholesterol values in the blood may be normal but more often especially in chronic myelogenous leukemia there is a reduction of cholesterol

Glucose is destroyed rapidly in the blood in chronic myelogenous leukemia in vitro immature and atypical cells hastening the process[4, 5, 51] In chronic lymphatic leukemia the glycolitic rate is not abnormal Oxygen consumption in leukemic blood in vitro is greater the more mature the cells while glycolysis is less the more mature the cells When studied under aerobic and anaerobic conditions glycolysis of immature myelogenous cells and lymphatic cells is that of young or embryonic tissue rather than of the type shown by cancer cells [53, 5] In vitro studies of tissue metabolism placing the cells under grossly abnormal conditions sometimes are difficult to evaluate or to transpose to conditions in the body

The same is true of tissue cultures of leukemic cells Mature forms polymorphonuclear neutrophiles monocytes eosinophiles and lymphocytes do not undergo further development but become necrotic in course of time Some of the grossly immature cells become transformed into other types such as phagocytes myelocytes giant cells plasma cells epithelioid cells monocytoid cells or fibroblasts Serum from leukemic blood having a high cell count causes a migration of leukocytes from the central clot in tissue cultures a property not marked in aleukemic sera There may be some difference in behavior movement of myeloblasts and lymphoblasts in vitro[55]

Grossly immature leukemic cells of the myelogenous group do not show the power of phagocytosis until they have matured to the stage of young neutrophiles The decreased ability of the immature cells to show ameboid movements and diapedesis or wandering through the tissues may account for their accumulation in the blood stream The mature polymorphonuclear leukocytes wander from the capillaries and find their way into the mouth and stomach where they are destroyed[6] After x ray therapy in chronic myelogenous leukemia the excretion of cells into the mouth is increased greatly with a corresponding decrease in the number of cells in the peripheral circulation

In films different cells show different degrees of resistance to crushing The large lymphocytes appear to be the most watery and crush easily Blasts are

teum[4] There may be pain around the joints pain in the long bones, periosteal reactions osteolytic lesions and bulky tumors of single bones[17]

Clinically there may be pain and tenderness of the long bones and gladiolus of the sternum, estimated to be present in 75 per cent of the patients with myelogenous leukemia[44] There may be thinning or destruction of the underlying bone or elevation of the periosteum by leukemic infiltration Osteosclerosis may be associated with myelogenous leukemia Osteomyelitis may follow tooth extraction or similar injury in patients with acute leukemia

Bone lesions either palpable or demonstrable by x ray occur more commonly in the head of the humerus and femur pelvis and vertebral column less frequently in the radius fibula and cranial vault and least frequently in the facial bones sterum ribs ulna, hands and feet[45]

Metastatic calcification may develop in the lungs, heart, adrenals, kidney thymus and moderate sized arteries[4] [4]

Chemical Changes

The abnormal growth of leukocytes is associated with several changes in the body metabolism The two principal features are the increased utilization of oxygen measured by the elevated basal metabolic rate, and the increased production of products of nuclear destruction phosphorus containing substances and uric acid

Forkner[4] [p 4] summarizes these changes as follows

1 The behavior of the chemical metabolism varies with the change in the disease picture and this explains at least in part some of the conflicting results reported in the medical literature

2 The nitrogen balance is variable in chronic leukemia and usually is negative in acute leukemia In general the leukocyte count and the nitrogen balance are reciprocal factors

3 The endogenous uric acid elimination and the uric acid and total nitrogen content of the blood generally are increased In cases responding favorably to treatment this increase usually is magnified although often not in proportion to the apparent amount of cell destruction brought about In general decreasing the leukocytes in the blood is accomplished by increasing excretion of uric acid

4 In chronic leukemia, untreated or not recently treated, there is usually a marked elevation of the blood phosphorus due to the total phosphorus content of cells especially immature white blood cells The phosphorus of the plasma varies greatly but remains within normal limits

5 Treatment of leukemia with roentgen rays or by means of radium results in a further increase of organic phosphorus in the blood and a transitory marked

of red or white blood cells The serum iron decreases with progressive deterioration of the patient and increases with a roentgen induced remission[31, 8, 83]

Basal Metabolism

In leukemia the basal metabolic rate as measured by the oxygen consumption is elevated in proportion to the activity of the leukemic process in the blood forming organs[5, 8, 57] It is not directly correlated with the height of the peripheral blood count or with the type of peripheral leukocytes except as they represent the predominant type in the hematopoietic tissues While the elevations in pulse rate loss of weight and irritability are similar to the condition in hyperthyroidism tremor is not common In leukemia there is economy of muscular movement on walking +12 to −33 per cent from normal as compared to an extravagance in muscular activity in hyperthyroidism 13 to 53 per cent above normal[1] The elevation of the basal metabolic rate in different patients with leukemia, depending on the severity of the disease process is from 13 to 60 per cent After x ray therapy there is a transient rise in the rate for one to three days followed by a rapid fall to normal limits when the response to treatment is good With the onset of a relapse the rate increases As the basal metabolic rate is proportional to the activity of the leukemia process it is a better guide to treatment than the peripheral leukocyte count

Serological and Immunological Changes

There is no characteristic increase in complement in leukemic blood Agglutinins do not develop as readily in leukemic blood after typhoid vaccination as in normal individuals or else they are destroyed more rapidly The heterophile antibody titer of leukemic sera is not abnormal contrasting with the high titers sometimes noted in infectious mononucleosis[63] While patients with chronic myelogenous leukemia develop high titers after receiving injections of horse serum as do normal individuals, patients with lymphatic leukemia do not[64]

Autoagglutination and heavy rouleau formation sometimes are marked in leukemia especially when the process is progressing and severe The cells of myelogenous origin show active proteolytic power even in the blast stage differentiating them from cells of lymphatic origin The polymorphonuclear and monocyte series of cells contain oxidases absent in lymphocytes

In chronic myelogenous leukemia there is an increased blood volume with high mean values for plasma volume especially in cases with anemia The total volume is higher in the absence of anemia In chronic lymphatic leukemia with leukocytosis the average blood and plasma volumes are increased[6]

quite resistant Young neutrophiles and eosinophiles evidently have a high water content and are easily mashed Mature neutrophiles, monocytes and lymphocytes are relatively not easily crushed X ray therapy does not appear to change the water content of the individual cell types the number of crushed cells not increasing in proportion to their numbers after x ray therapy of the patient

Other Chemical Features

The blood glutathione oxidized, is increased in amount in myelogenous leukemia but is reduced or absent in the lymphatic type Occasionally Bence Jones protein is present in appreciable amounts in the blood plasma and urine The blood iodine is increased in about 40 per cent of the patients with lymphatic leukemia and in some patients with myelogenous leukemia The amount is not comparable to the elevation of the basal metabolic rate [9]

There are usually low values for coenzymes I and II in the whole blood[63] Hypercalcemia is noted in some patients In patients with bone involvement there is a slight elevation of the serum phosphatase, 5 to 15 units [0] The nucleotide nitrogen content of the blood in leukemia is elevated when the leukocyte count is high having in myelogenous leukemia an average for males of 7 36 mgm per 100 c c of blood as compared to a normal of 6 2 mgm and an average for females of 5 84 mgm per 100 c c as compared with a normal of 5 2 mgm [71]

A gel forms when congo red is mixed with leukemic blood The oxidation reduction potential values for leukocytes in leukemia are abnormally high above the normal of 12 5 to 17 5 (aerobic) and 11 to 12 (anaerobic)[73] The nucleus of myeloblasts has a pH of 6 5 and the cytoplasm of 6 4 being more acid than mature neutrophiles of healthy men in whom the nucleus has a pH of 6 7, the cytoplasm of 6 6 and the granules of 7 1 Lymphocytes and monocytes also have an acid reaction but the granules of eosinophiles are slightly alkaline (pH 7 18)[74]

Leukemic leukocytes especially lymphocytes dehydrogenate fatty acids, and keto acids acetic are formed Unusually high values for reduced cevitamic acid are found in analyzing the whole blood of patients with leukemia in whom the leukocyte count is elevated [8] There is an increased utilization of ascorbic acid in leukemia[78] The relation of cholesterol to non cholesterol fractions of the serum is very high owing to the extremely low values for the latter fraction[79] The blood histamine may be increased one hundred times the normal in chronic myelogenous leukemia but not in the lymphatic form [9]

The iron content of the serum is normal or high in chronic leukemia, but in myeloblastic leukemia the serum iron decreases when the body temperature becomes elevated The iron content of the serum is independent of the number

High Blood and Urine Uric Acid

Uric acid is an end product of nuclear destruction and it is greatly increased in leukemia There may be gout like symptoms but renal calculus formation is rare presumably because the uric acid is held in solution in the urine as a salt

High Basal Metabolic Rate

The mechanism of the production of the high basal metabolic rate i e increased absorption and utilization of oxygen is not clear The effects in leukemia differ from those in hyperthyroidism[9] although iodine or removal of the thyroid tends to lower the rate

The increased utilization of oxygen may be related to the increased nuclear destruction [4] and although it is highest when the leukemic process is most active in the blood forming organs it does not seem likely that the use of oxygen by the actively growing and dividing cells accounts for the abnormal amount consumed The actual volume of the new tissue is however considerable and this must be one factor as decrease in volume with x ray or arsenic causes a fall in oxygen consumption All other abnormal factors are however decreased at the same time by this therapy

Leukocytosis and Leukopenia

The problem of why one patient presents a leukocytosis while another is aleukemic subleukemic with the same degree of involvement of the hematopoietic organs has been a source of much speculation One factor appears to be the lack of metastatic foci of growth in moving organs as the lungs in the aleukemic individuals Such patients who were known to be aleukemic on the day of death showed very few foci of growth in the lungs liver or kidneys Growths in the marrow are protected extremely thoroughly by the solid walls of bone whereas growths in the lungs are massaged eighteen or more times per minute with a corresponding effect on the liver and abdominal viscera Immature cells are not protected and they may enter the blood stream The disorderly fashion in which cells enter the blood not necessarily in the order of maturity but in all stages suggests a mechanical factor in pushing them into the circulation rather than a maturation release The presence of leukemia patients with a wide gap in the type of cells extremely immature forms and mature forms with practically no intermediate stages suggests that one focus is producing blasts while another is producing fairly mature cells

Mechanism of Production of Symptomatology

Anemia

Several factors appear to enter into the production of anemia in leukemia The bone marrow becomes crowded with rapidly growing and immature white blood cells and the proliferation and delivery of red blood cells are defective This is especially marked in lymphatic leukemia where the lymphocytes invade the bone marrow, and the degree of anemia is a fair measure of the amount of involvement of the marrow tissue

The deposition of iron in the tissues suggests hemolysis as a factor The icterus index is not constantly elevated however and evidences of hemolysis are not prominent There may be destruction of the precursors of hemoglobin they being unused because of the failure of many red blood cells to complete their maturation

Hemorrhage plays a part in the production of the anemia, especially in the acute forms and late in the chronic types The loss of blood is not compensated for by adequate regeneration because of the leukemic abnormality of the bone marrow

Hemorrhage

In acute leukemia and in chronic lymphatic leukemia the crowding or replacement of the marrow by the rapidly growing cells prevents the production of blood platelets This is associated with a tendency to capillary hemorrhage and a failure of the blood clot to retract

In chronic myelogenous leukemia associated with the unusual stimulation of all types of cells in the marrow the platelets usually are increased in number The tendency to bleed under these circumstances appears to be caused by the failure of the clot to retract adequately because of the mechanical interference of the many leukocytes This factor also is present in lymphatic leukemia when the white blood cell count is high

At times the tendency to bleed appears to be related to additional factors There is increased capillary fragility and the slightest trauma causes a crop of petechial hemorrhages to appear in the skin and internal organs

The spongy bleeding gums remind one of scurvy and non availability of vitamin C may be a factor in their causation Invasion and damage of the liver are associated with a fibrinogen defect in some individuals There are, no doubt other factors at present unknown

limitation in the movement of the diaphragm with reduction in the vital capacity The displaced apex with dyspnea and a hemic murmur from associated anemia often leads to a diagnosis of a cardiac lesion

A grossly enlarged spleen may cause congestion of the abdominal or leg vessels by direct pressure This may result in pain in the left leg and edema The spleen may be enlarged to two or three times the normal volume and four times the average weight without being palpable A palpable spleen is not always enlarged It may be pushed down by a low diaphragm Palpability of an enlarged spleen depends largely on whether it is hard or soft tensely distended or relaxed

The innervation of the spleen is important from the point of view of symptom production While the spleen itself is insensible to pain stimuli pain often is referred to this region The sympathetic nerves of the spleen arise from the third to the tenth thoracic segments The vascular innervation is from fibers from the third to the twelfth thoracic and the first to the fourth lumbar segments through the semilunar, celiac, ganglion Fibers from the vagus also enter the spleen

These fibers constitute the intrinsic innervation of the spleen but an additional group outside of the spleen is affected when the organ is enlarged Through its attachment to the outer part of the diaphragm the local intercostal nerves are involved When the spleen enlarges the central part of the diaphragm innervated by the phrenic nerve from the third fourth and fifth cervical segments is involved Some of the fibers of the phrenic nerve run to the outer part of the diaphragm

The symptoms which can arise from direct stimulation of the nerves or from referred or reflex action are many[a] When the spleen enlarges the constant irritation of the segments of the spinal cord with which the nerves are associated causes the other nerves from these regions to be hypersensitive Thus the intercostal nerves of the region register tenderness referred to the skin of the lower left part of the chest Through the phrenic fibers the cervical cord becomes sensitized and the skin of the left shoulder and sternal region shows tender points

There may be pain in the left shoulder In one patient with chronic myelogenous leukemia it was limited to an area about 2 5 cm in diameter over the anterior surface of the deltoid It was dull and continuous in character and not aggravated on motion of the shoulder joint This pain was a source of great discomfort and repeated x ray studies failed to show any bone or arthritic involvement Local applications were ineffective but the pain subsided upon reduction in the size of the spleen with x ray therapy

Areas of referred pain may be in the cervical region over the trapezius muscle

Pain and Other Symptoms

Pain in leukemia usually is due to pressure, invasion, or it is of the referred type In periosteal invasion the periosteum is elevated by growths of leukemic cells These nodules are extremely tender and cause a considerable amount of pain The periosteal involvement may appear in any bone and may involve different bones in succession

The enlarged spleen and liver may give rise to local and referred symptoms These include pain in the left upper quadrant abdominal discomfort dragging feeling in the left or right upper quadrant of the abdomen mid epigastric pain jaundice pain on deep inspiration tender spleen and difficulty in bending

Other symptoms referred in nature are dizziness or giddiness, headache constipation diarrhea vomiting nausea cough palpitation anorexia fever pain in the left or right shoulder pain in the left side of the chest, pain in the back pain in the left leg pain in certain positions night sweats, hemorrhoids chills buzzing in the ears gastrointestinal upsets tenderness of the trapezius or deltoid muscles dysphagia soreness of the inner surface of the left thigh tightness of the left knee swollen left testicle, friction rub in the left axilla pain in the left arm visual disturbance and the left pupil smaller than the right To these may be added the unusual frequency of left otitis media

Some of these symptoms are produced by mechanical pressure of enlarged organs or lymph nodes Others are produced or aggravated by myocardial insufficiency and anemia A group however is secondary to the peculiar innervation of the spleen liver and diaphragm called into play when these organs are pathological

The normal spleen is suspended in the upper left corner of the abdomen in contact with the diaphragm on its outer and upper surface lateral to the region of the cardiac apex It is suspended by filmy bands attached to the stomach diaphragm and colon When the spleen is enlarged the adhesions to the diaphragm may become more extensive involving the central as well as the lateral area of this organ This feature is important in the production of certain symptoms Occasionally the suspensory ligaments are stretched or elongated and the spleen may descend even into the pelvis

The position of the enlarged spleen accounts for some symptoms There may be a feeling of fulness after the ingestion of a small amount of food, and pressure on the colon and intestines may be factors in the production of constipation or diarrhea The upward displacement of the diaphragm causes the cardiac apex to deviate to the axillary line, especially when the patient is lying down The patient may be conscious of his heart beat, there may be precordial pounding or palpitation and occasionally dyspnea There may be an actual

all cell types being involved As the disease progresses one type the neutrophile or the monocyte increases in number with a normal development First there are an unusual number of mature forms later an increase in immature form is recognized the number of blasts is increased and mitosis is common

In the full blown chronic myelogenous or monocytic leukemia there is very active cell division with a filling up of the marrow causing the fat to be reduced to small globules or in some areas to be entirely displaced As a rule all cell types appear to be growing rapidly including the red blood cells in addition to the particular cell type involved in the leukemic process Late in the disease the number of cells in the blast stage increases and the terminal picture if the patient lives until the evolution is complete is that of an almost pure population of cells in the blast stage with suppression of all other cells In acute types of leukemia the transformation into the blast stage is rapid and the other cells are suppressed quickly The degree of filling of the marrow is shown by the blocking of the venous sinuses so that it is not possible to give a transfusion via the marrow in the advanced stages

In chronic lymphatic leukemia the marrow remains normal for varying periods until there is invasion with lymphocytes There is still an uncertainty as to whether lymphocyte growth starts de novo in the marrow or whether it is metastatic The lymphoid tissue gradually fills the marrow spaces with ultimate suppression of the normal marrow cells Thus the degree of anemia is a fair measure of the extent of the invasion of the marrow

After x ray or radium therapy or arsenic as Fowler s solution there is first ar increased growth rate with an increase in the number of mitotic figures followec

TABLE IV

CHRONIC MYELOGENOUS LEUKEMIA

Peripheral Blood

Day	Leukocytes per cu mm	X ray
−2	2 4 600	
−1	247 600	
0	242 800	200 r over spleen
1	278 800	200 r over spleen
2	261 200	200 r over spleen
3	202 400	
23	0 100	
51	10 250	
7	11 500	

in the epigastrium and in the lower costovertebral region posteriorly Through the vagus pathways the nucleus of the vagus may become hypersensitive as well as the associated nuclei fifth nerve Dizziness or giddiness may be a symptom as well as nausea and vomiting, headache and cough In these cases it had been assumed that the symptoms were secondary to some unknown feature of the underlying disease In patients with anemia one would think of some chemical disturbance associated with an oxygen defect but the presence of some of these symptoms in non anemic individuals suggests the role of the referred symptoms on a basis of the type of innervation Foerster[87] was able to produce nausea and vomiting when he stimulated the central ends of the cut vagus below the diaphragm

While the basis of the symptoms of feeling of fulness in the left upper quad rant pain and a dragging sensation in this region would at first seem self evident, *yet the absence of sensation in the spleen itself and its total lack of pain*, when stimulated suggest that there may be a referred basis for these sensations Some patients show enough symptoms attracting the attention to the chest to have an x ray examination without however any positive lesions being found

The acute pain associated with splenic hemorrhage or infarction usually is attributed to stretching of the capsule or to peritoneal involvement The mechanism must be of a referred type as is noted when there is skin tenderness over inflamed abdominal viscera[88]

Fever

Fever usually is present at some time during the course of the disease and is generally a marked feature during the terminal stages Its origin and mechanism are not understood at present When a remission is produced with x ray or arsenic the temperature returns to normal There is no definite pattern the temperature being high or low at different times of the day in different patients Some individuals show a tendency to relapses and remissions as far as fever is concerned there being a week or two with fever followed by days or a week or more of normal or but slightly elevated temperature The Pel Ebstein type of fever of Hodgkin s disease is not present The fever in acute fulminating leuke mia may be extremely high In chronic leukemia in remission the temperature usually is within normal limits but careful determination of the temperature during this period often will show mild elevation in the early evening

The Hematopoietic Organs in Leukemia

The earliest changes in the bone marrow in developing leukemia are an ac centuation of normal processes The bone marrow appears hyperactive usually

As the disease progresses the total number of leukocytes increases either gradually or rapidly It is not unusual for the white blood cell count to reach from 100 000 to 500 000 per cu mm Counts of over 1 000 000 have been recorded The count may vary considerably from day to day up or down and there is considerable hourly variation even without any special form of treatment

In the beginning the cells show progressive immaturity usually in an orderly manner Thus at first practically all of the neutrophiles are mature later the number of young neutrophiles increases followed by an increment in the number of metamyelocytes myelocytes and finally blasts In some patients the change is not so orderly but blasts appear early side by side with the mature forms This condition is called hiatus leukemicus by Naegeli This may be an indication of an advanced leukemic focus somewhere in the body while much of the hematopoietic tissue still is normal As a rule however the leukemic process in the advanced stages is in about the same stage in all the bones However great variation is noted from one patient to another

With the crowding of the marrow immature red blood cells monocytes platelets megakaryocytes and grossly atypical cells are pushed out and appear in the blood stream Part of the mechanism of the appearance of immature cells in the blood stream is the instability of metastatic foci in soft moving or pulsating organs as the lungs liver and kidneys The bone marrow cells normally are protected by the hard bone walls and are subjected to the least disturbance of any cells in the body When marrow grows in the lungs the tissue is subjected to massage at least eighteen sometimes more times a minute The disorderly delivery of cells into the blood stream is shown by the presence of normoblasts with but few reticulocytes If the delivery had been in the order of maturation the reticulocytes would have been increased in number to 15 or 20 per cent before nucleated red blood cells appeared The presence of immature monocytes makes the diagnosis difficult at times as the question of myelogenous or monocytic leukemia is presented The picture may vary from month to month With the crowding of cells in the hematopoietic organs and the growth and storage of cells in unusual places tissue spaces sinusoids intercellular infiltration grossly abnormal forms appear Thus while the first changes are quantitative the later stages show qualitative alterations Among the changes are failure of the nuclei to segment although the chromatin assumes the mature characteristics The cytoplasm in some cells may show gross immaturity while the nucleus shows changes of older cells Forms may show no granules when they are expected or non granular forms may show granules Cells in stages of mitotic division may appear in the blood stream The number of chromosomes may appear to be twenty four instead of forty eight According to some this repre

TABLE IV (*Continued*)

Bone Marrow (Biopsy)

	Before X ray	After X ray
Total leukocytes	24 000	20 000 per cu mm
Polymorpho neutrophiles adult	56 800	8 300
Polymorpho neutrophiles young	83 500	4 800
Metamyelocytes	14 700	3 100
Myelocytes	6 600	400
Myeloblasts	6 000	00

in the subsequent days by an orderly maturation of the cells with a decreased rate of new cell production No areas of necrotic cells are found nor do the cells show degeneration phenomena In the early stages of the disease the marrow returns practically to normal except for an increase in the number of eosinophiles and basophiles These changes are shown in Table IV[13]

In subsequent relapses sooner if there has been much x ray therapy the number of blasts increases and persists After each series of x ray treatments in the patients with progressive disease the blast population becomes more predominant There appears to be a change in the nature of the cells and they behave more as neoplastic tissue making one speculate as to the possibility of neoplastic conversion by x ray therapy

In acute leukemia after x ray therapy the cells do not decrease in number but are found filling the marrow at death and they do not appear to be necrotic Thus a boy 8 years old who had acute lymphatic leukemia of three weeks' duration received fourteen x ray treatments During this period his leukocyte count increased from 77 000 per cu mm to a maximum of 216 000 per cu mm The sternal bone marrow at death showed 90 700 primitive blasts or stem cells per cu mm 319 000 lymphoblasts 134 000 large lymphocytes and 30 000 small lymphocytes per cu mm Normally the only lymphocytes would have been those in the circulating blood

Blood Changes in Chronic Myelogenous Leukemia

In patients with chronic myelogenous leukemia whose blood had been studied at frequent intervals early in the disease several pictures may be noted Some show but little change in the beginning occasionally an increase in the number of mature neutrophiles Some start with a picture resembling pernicious anemia, develop leukocytosis after months or years and then the complete leukemic blood A few have started as polycythemia evolving into leukemia erythroleukemia[17]

Blood Changes in Chronic Monocytic Leukemia

Monocytic leukemia runs a course much like the myelogenous type and the earlier studies group d the two diseases together In true monocytic leukemia Schilling type there is a progressive increase in the number of mature monocytes in the blood stream followed by the appearance of more and more immature forms As the marrow becomes crowded immature neutrophiles and red blood cells may be extruded into the blood stream giving rise to the appearance of both myelogenous and monocytic leukemia Naegeli type of monocytic leukemia (The name myelogenous as applied only to neutrophile leukemia is now somewhat confusing as the monocytes also ari e in the marrow)

The earliest stages of monocytic leukemia may show a slow increase in the number of monocytes in the blood but the p cture may start with anemia which resembles pernicous anemia closely both in morphology and therapeutic response

True monocytic leukemia does not show a marked decrease in the number of cells after x ray therapy and the response is slower and not as regular as in the chronic myelogenous form When the cells are fairly mature arsenic in the form of Fowler s olution may cause a rapid fall in the number of cells

The total leukocyte count usually is low at the beginning of the disease (1 000 to 4 000) but may rise to 500 000 at times Severe anemia 1 000 000 to 2 000 000 red blood cells per cu mm, may develop

As the disease progresses the number of young monocytes increases then a stage is reached with a cell which may be called metamonoblast a cell resembling the promyelocyte with blue staining cytoplasm and fairly large reddish blue staining granules Finally the monocyte blast appears which resembles the myeloblast in morphology and staining characteristics, but early in the development it shows a single granule staining reddish blue This later become multiple and the granules cover almost the entire cell As the cell matures the granules become smaller and stain red characterizing the young monocyte

Large hemohistiocytes of Ferrata may be noted in the blood film They may be slightly mashed or spread out metamonoblasts or promyelocytes or they may be a distinct group of cells These sometimes are seen also in myelogenous leukemia

The monocyte group of cells usually is oxidase positive although individual oxidase negative cells are encountered

Blood Changes in Chronic Lymphatic Leukemia

In the earliest stage of chronic lymphatic leukemia there is a relative lymphocytosis which later becomes absolute As a rule the number of small lympho

sents a reduction in number, while others consider that it represents a form of doubling of chromosomes Amitotic division, possibly an artifact, has been described

The terminal stages are marked by increasing numbers of myeloblasts and stem cells until finally this type of cell predominates At this stage the marrow is filled with blasts, and red blood cells, platelets and monocytes decrease in number in proportion to the encroachment on the space The anemia may be extremely severe in the terminal stages, and the red blood cell count may fall to 500 000 per cu mm The decrease in number of platelets is reflected in the bleeding tendency

The anemia is a variable feature of the disease and may appear early or late Some patients have white blood cell counts of 100 000 per cu mm for one or more years with normal red blood cell counts Eventually nucleated red blood cells appear and anemia becomes a progressive feature The hemoglobin may be reduced in proportion to the decrease in the number of red blood cells color index = 1, or there may be iron deficiency Some show macrocytosis of the red blood cells although this is not an invariable feature Poikilocytosis is not present constantly and varies in different individuals

The changes after x ray or radium therapy are discussed under treatment There is a temporary increase in number during the first twenty four hours followed by a decrease The changes after arsenic therapy are similar, except that the process may be somewhat slower With clearing out of the marrow there is improvement in the maturation of the red blood cells as well as of the white cells and an increase in the number of reticulocytes may be noted in the peripheral blood for days or weeks during the beginning of the remission

The different stages of the cells in the development of the neutrophile show the oxidase reaction with the exception of the most primitive stem cell or blast

In the *aleukemic* or *subleukemic type of the disease* the leukocyte count may be normal or low Usually there is a disturbance in the differential leukocyte count, and a few grossly abnormal or immature forms may be noted As the disease in the marrow appears to be identical with that of the leukemic type the progress of the anemia is the same The aleukemic forms may become leukemic occasionally not until a day or so before death Diagnosis of aleukemic leukemia is greatly facilitated by finding a hypertrophic bone marrow on sternal puncture with an increase in the number of cells in mitosis and an unusual number of blast forms

As myelogenous leukemia develops especially after x ray therapy, the number of eosinophiles and basophiles increases In remissions induced by x ray or arsenic the predominant abnormality in an otherwise fairly normal blood may be an increase in the number of eosinophiles and 4 to 5 per cent basophiles

range of 15 000 to 50 000 per cu mm with an increase to 00 000 or more in the terminal stages Some patients run an aleukemic or subleukemic course throughout

There is a rap d appearance of blasts without a long p riod with intermediate forms hiatus leukemicus of Naegeli Because of the difficulty in determining the type of blast present many cases of the myelogenous typ have been classified as lymphatic

The cells do not decrease in number after x ray therapy but actually increase rapidly Anemia develops rapidly and may be extreme y severe With the crowding out of the red blood cell tissue in the marrow the platelets are suppressed also and a marked hemorrhagic tendency develops Some patients show an atypical form of blast with notched or folded nuclei and a varying amount of basophilic cytoplasm in the cells

Clinical History and Course of Chronic Myelogenous Leukemia

The onset of chronic myelogenous leukemia usually is insidious and it is discovered sometimes by accident during an examination for trauma or for an operation The first symptom in most patients is ease of fatigue The dis eas may be quite far advanced without many appreciable symptoms With the or t of an enlarged spleen or enlarged lymph nodes pressure symptom begin to appear Late in the disease anemia is an important factor as is cachexia Th basal metabolic rate is elevated early and there is nervousness irritability and loss of weight A tendency to bleed is a late symptom

The symptoms vary greatly in different patients both in evolution and in severity They are usually more accentuated as the terminal stage approaches and fever becomes more constant There may be afternoon elevations to 10 F to 104 F

Th re i a tendency for the spleen to become larger as the disease develops and the liver increases in size The spleen may reach to the pelvis and extend beyond the midline to the right Marked ascites is rare but there may be accumulations of a small amount of fluid during the terminal stages in the pleural pericardial and peritoneal cavities

During induced remissions the patient may enjoy excellent health and be able to carry on his ordinary work In some the ease of fatigue remains although less marked than before therapy

With the onset of a relapse there is an elevation of the leukocyte count and an increase in the degree of anemia The symptoms return often with new additions As a rule each remission is shorter than the previous one although there are marked exceptions One patient under study at pre ent had a remission of

cytes increases first later the medium sized and large forms and terminally, the blasts With encroachment on the bone marrow there is progressive anemia and thrombocytopenia in proportion to the reduction in the marrow space While total white counts of 1 000 000 per cu mm have been noted, and some higher counts have been reported, the average patient shows from 50 000 to 100 000 cells per cu mm

After x ray or radium therapy there is progressive reduction in the number of cells the rate being proportional to the number of small lymphocytes present The response is less rapid or complete when the cells are large lymphocytes and there may be no appreciable reduction when the bulk of the cells are blasts

The aleukemic forms show a normal or low peripheral leukocyte count at times with a predominance of lymphocytes and an occasional nucleated red blood cell Anemia may be a marked feature necessitating the differential diagnosis from pernicous anemia and other types Bone marrow material obtained on sternal puncture will show the marrow invaded by lymphocytes The aleukemic form may develop a leukocytosis in the course of its evolution

The cells of the lymphatic series are oxidase negative Plasma cells commonly are present in the blood stream and grossly atypical forms of lymphoid cells with notched nuclei may be present

Types of Lymphatic Leukemia

There are at least two clinical and hematological types of lymphatic leukemia The first which may be called lymphocyte leukemia is characterized by extensive involvement of the peripheral lymph nodes and the predominant cell is the round nucleus type of small lymphocyte The nucleus usually measures about 7 5 microns The second type may be called splenocyte leukemia and is characterized by a large spleen occasionally reaching into the pelvis without gross enlargement of the peripheral lymph nodes The characteristic cell in this type is slightly larger than the lymphocyte and has an oval or kidney shaped nucleus

Blood Changes in Acute Leukemia

The predominant cell in acute leukemia is the blast or stem cell It is sometimes impossible to tell its type as all of the stem cells are oxidase negative Other cells present in the blood stream may give a clue to its myelogenous lymphatic or monocytic nature or it may belong to still other groups '

The total leukocyte count may be low in the beginning and may remain so or increase to as high as 1 000 000 per cu mm Most of the patients show a

larged A hemic systolic murmur may be present when there is anemia The heart rate becomes rapid but the rhythm usually is not disturbed As a rule the blood pressure is not elevated and hypotension has been encountered more frequently than elevated pressures

Spleen — The spleen usually enlarges early in the course of the disease and may reach the pelvis and extend to the right of the midline It is quite firm and smooth with an easily palpated edge and the notches can be felt Characteristic symptoms outlined earlier in this chapter develop Splenic infarction or hemorrhage may cause pain tenderness enlargement friction rub and elevation of body temperature Splenic rupture is an occasional complication A sudden progressive enlargement of the spleen may accompany a relapse or increased virulence of the disease The chronically enlarged spleen does not pulsate or vary in size during meals as does a normal spleen The size of the spleen may be reduced greatly by x ray radium or arsenic therapy in the early stages less markedly however in the later stages of the disease A number of cases have been reported in which the spleen did not enlarge until late in the course of the disease

Liver — The liver usually enlarges but not to the extent of the spleen The edge is firm and not tender unless there has been a sudden increase in size The liver usually is crowded by the large spleen and the left lobe especially is displaced Jaundice is not common but appears when obstructive lesions develop

Gastrointestinal System — The appetite may be good or poor The crowding of the abdomen leads to a feeling of fulness in the epigastrium with belching nausea or vomiting Many times the vomiting follows coughing and may be associated with thick mucus in the posterior pharynx Constipation often is associated with the lack of solid food eaten and may be a very troublesome feature Diarrhea is less frequent sometimes associated with the leukemic process at other times with one of the effects of treatment arsenic Bleeding may be reflected in hematemesis or blood in the stools

Urine — Kidneys — Bladder — The urine may contain albumin and casts occasionally an increase in leukocytes of the leukemic types Hemorrhage from the kidney or bladder with blood in the urine is not uncommon in the later stages Prostatic infiltration may make urination difficult and frequency and nocturia may be features Large amounts of uric acid with the development of heavy sediments reflect the abnormal nuclear katabolism Bence Jones protein has been found in the urine of some of the patients

Sexual Organs — Priapism has been discussed as a rare symptom Menorrhagia is common when there is a bleeding tendency often with metrorrhagia Amenorrhea may be an early symptom often persisting until the hemorrhagic tendency develops X ray treatment may disturb the menstrual cycle Irreg

two months following the first x ray treatment four months after the second and after a remission induced with arsenic there has been no recurrence for over a year[91]

Death may be from acute or chronic hemorrhage, infection pneumonia or cachexia Sometimes death comes suddenly from cerebral hemorrhage, or there may be a slow period of physical deterioration There may be extremely high body temperatures near the end of the disease

Physical Condition

There is often a peculiar uniform pallor which enables some physicians to suspect leukemia Evidence of loss of weight slight in the beginning becomes marked as the disease progresses The patient may appear perfectly well during an induced remission in the early stages

Eyes — There may be marked pallor of the conjunctivae, occasionally congestion Retinal hemorrhages are not uncommon with blurring of vision[9, 91]

Ears — There may be slight impairment of hearing occasionally deafness Meniere s syndrome associated with labyrinthine hemorrhage may be present Otitis media ossificans may develop with fibrosis and ossification in the hollow parts of the labyrinth and atrophy of the auditory nerve endings Tinnitus described as buzzing may be very troublesome at times

Nose — Not many symptoms are attributable to the nose Epistaxis is a feature during the hemorrhagic period There may be a heavy mucoid or mucopurulent discharge

Mouth — Late in the disease the gums become spongy and bleed easily Areas of the mucous membranes become infected and necrotic The teeth may become loose and the gums infected

Pharynx — The tonsils and adenoid tissue seldom are grossly enlarged Punctate hemorrhages may appear on the mucous membranes associated with pain and dysphagia Hoarseness may develop There may be a postnasal discharge of thick mucus

Tongue — The tongue usually is heavily coated It may be dry with beefy edges in the toxic states

Lymph Nodes — The disease may be far advanced without evident enlargement of the peripheral lymph nodes In some individuals however, they become quite large discrete firm not tender

Lungs — There is frequently a hard paroxysmal non productive cough associated with enlarged hilar lymph nodes The vital capacity is reduced by the upward crowding of the abdominal organs as well as by pulmonary congestion

Heart — The apex is displaced upward and to the left when the spleen is en

Clinical History and Course of Chronic Lymphatic Leukemia

The course and onset are much like that of chronic myelogenous leukemia. The lymph nodes enlarge early in the disease and splenomegaly usually is not as marked as in the myelogenous form. An elevated basal metabolic rate with its attendant symptoms is characteristic and loss of weight with ultimate cachexia is common. However during the course of the disease especially in the slowly evolving types nutrition may be excellent. As with the myelogenous type the symptoms vary markedly from patient to patient. There is usually ease of fatigue and increasing weakness.

Physical Condition

The changes in the different systems are much like those in chronic myelogenous leukemia with certain variations as noted below.

Eyes — Leukemic infiltration of the lids has been noted. Occasionally orbital tumors cause exophthalmos. The leukemic hemorrhages are like those in the myelogenous form.

Ears — Deafness is slightly more common in the lymphatic type than in the other forms of leukemia.

Pharynx — The leukemic process may be very marked in other parts of the body without gross involvement of the tonsils or pharyngeal adenoid tissue. Petechial hemorrhages are common.

Mouth — The changes are much like those in myelogenous leukemia especially in the later stages.

Lymph Nodes — This type of leukemia is characterized by the greatest involvement of the peripheral lymph nodes. In the early stages the enlargement may involve only one group of nodes but later nodes in all areas are hypertrophied. The nodes are fairly soft, discrete, not tender or adherent to the skin or surrounding structures. Matting together may result from growth pressure or from secondary infection. A few cases have been recorded in which no adenopathy was found at autopsy[7, 8].

The enlarged cervical lymph nodes may cause limitation of motion of the head and gross disfigurement. The axillary enlargements cause considerable discomfort. Dyspnea, cough and dysphagia may accompany enlargement of mediastinal nodes. Enlarged abdominal nodes may be associated with diarrhea or with ascites.

Heart, Lungs, Liver, Kidneys — The signs are like those of chronic myelogenous leukemia. The liver enlargement usually is less than that of the spleen.

Spleen — The spleen may enlarge early and be easily palpable. Enormous

nancy may run a normal course with normal uncomplicated delivery Abnormal bleeding is not a troublesome feature, as a rule

Extremities — Thrombophlebitis is a rare complication There may be many purpuric areas and skin lesions present on the skin

Nervous System — The nervous system changes have been reviewed The most common symptoms, often due to multiple causes, are headache, nausea vomiting paralysis or palsies of almost any nerve from leukemic infiltrations or hemorrhages paresthesia numbness tingling and sensations of pain Symptoms vary with the nerve group involved There may be meningitis like episodes and very high temperatures Herpes zoster is more common in leukemia than in a similar non leukemic group of patients

Skin — The skin lesions have been discussed already in a section under the general heading, Symptomatology and Pathological Changes There are many types the most common being associated with petechial hemorrhages Pruritus may be a troublesome feature

Fever — Fever is a characteristic symptom and appears at some time during the course of the disease There appears to be no regular pattern In some patients there is an afternoon rise to 99° to 100° F A number of patients have shown periods of increasing fever with daily increments until 104° to 105° F is reached then gradual decrease until a fairly normal temperature curve at least not above 99° F is reached This episode may last for one to three weeks with a similar remission period before the next relapse develops The temperature curve may not be regular, and the highest point in any twenty four hour period may be reached at any hour of the day or night instead of during the afternoon or evening During the twenty four hour period usually there is considerable fluctuation from normal seldom from subnormal to high points

Fever usually indicates an exacerbation of the leukemic process and when it is high the immediate prognosis is poor Contrary to a current conception fever in itself is not a contraindication to x ray therapy However, it may be associated with a blast predominance in the blood or marrow, in which case the type of cells is the factor which would make one avoid irradiation therapy

Emotional Features — The role of emotional factors in leukemia is an interesting problem The high basal metabolic rate may be associated with emotional instability nervousness irritability and mental changes However, a relapse has often been noted to follow severe emotional shock e g , sudden death of a parent sudden business reverses worry over induction of a son into the army, etc The difficult problem here is the evaluation of the cause and effect The relapse may have begun and the emotional crisis which would have been weathered by a normal individual may seem to be the precipitating factor because of the abnormal irritability or sensitivity of the patient

The use of sternal spleen and lymph node puncture has greatly facilitated the diagnosis of leukemia or its elimination in cases simulating some of its features The specific cell type and the high dilutions of serum in which sheep cells are agglutinated heterophile agglutination help to diagnose infectious mononucleosis In septicemia and pyogenic infection with leukocytosis there is usually extreme basophilia of the granules of the neutrophiles

Duration and Prognosis

The average duration of chronic myelogenous leukemia in cases treated by x ray or radium and in a group not treated by irradiation is shown in Table V

TABLE V

Age	Treated by Irradiation Av Duration in Years	Not Treated by Irradiation Av Duration in Years
1–10	2 0	
11–20	3.41	2 50
21–30	3 43	3 72
31–40	3 66	2 66
41–50	4 00	3 73
51–60	3 64	2 01
61–70	2 34	2 70
Average	3 5	3 04

While in this series there was but slight advantage in favor of treatment by irradiation it is generally agreed that the life of the irradiated group is more efficient and there is a shorter period of invalidism and suffering considering the course of the disease as a whole It is possible that the more modern statistics will show a considerable increase in the life span of properly treated cases In the series cited above there was an improvement of one year in the total duration peak of the distribution curve when the treatment was started in the first half of the disease when compared with those first treated in the second half of the disease

In chronic lymphatic leukemia the average duration of life after the first symptom was 3 45 years being essentially the same in irradiated and non irradiated cases[1] Irradiation causes little improvement after the hemoglobin falls below 50 per cent when there is marked thrombocytopenia or when there are many blasts in the blood or hematopoietic organs

In chronic monocytic leukemia most of the reported cases have had a shorter

sizes, like those attained in chronic myelogenous leukemia are reached only occasionally The surface remains smooth, and the notches are retained Pain and other features are like those in chronic myelogenous leukemia

Gastrointestinal System — As in myelogenous leukemia many and varied symptoms may be the result of involvement of the gastrointestinal tract[31 97] The enlarged lymph nodes in the intestine, mesentery and lumbar region give rise to obstructive symptoms

Sexual Organs — Priapism has not been reported in this form The irregularities of the menstrual function are as in the myelogenous form Pregnancy is much rarer in the lymphatic form, most of the cases of pregnancy having occurred in the myelogenous variety

Nervous System — The changes are like those described in myelogenous leukemia Herpes is not an infrequent complication

Skin — The skin lesions are of many types Pruritus is present almost invariably at some time in the disease and may be the outstanding symptom

Bones — Marked changes appear in a few patients Tenderness and pain occur less frequently in the lymphatic than in the myelogenous type[44 9 98]

Fever — Temperature changes occur as in the myelogenous form

General Symptomatology and Hemorrhagic Phenomena — The general symptomatology and hemorrhagic phenomena are as in myelogenous leukemia

Physical Condition in Chronic Monocytic Leukemia

Changes in the organs similar to those in chronic myelogenous leukemia are noted

Mouth lesions with white necrotic areas are more common in this form The peripheral lymph nodes seldom are enlarged The liver and spleen usually are enlarged to about the same degree differing from the excessive enlargement of the spleen in chronic myelogenous leukemia Cutaneous lesions of many types are encountered[39 1 0 1(1 10 104]

Differential Diagnosis

Leukemia at some stage may be confused with many diseases either because of enlarged lymph nodes liver and spleen as in Banti s syndrome cirrhosis of the liver, types of lymphoma all types of infective and other splenomegalies or subacute bacterial endocarditis or because of the blood picture as in infectious mononucleosis extreme leukocytosis in infections tuberculosis Hodgkin s disease measles, pertussis mustard gas poisoning agranulocytosis myeloma hemorrhage added to infection erythroblastic anemia and the various types of erythroblastosis, neoplasms involving the bone marrow and osteosclerosis[143]

higher the number of blasts the les the desirability of using x ray therapy and when the percentage is over 10 it is not wise to use this type of therapy unless immediate symptomatic relief is imperative

When the symptoms are mild it is probably well to start with Fowler s solution and turn to x ray only if the condition cannot be controlled

Principles of Treatment

Treatment involves the use of x rav radium or radioactive substances arsenic and blood transfusion Anemia is to be treated primarily by clearing out the bone marrow to give the red blood cells room to grow Blood transfusion gives valuable symptomatic but only temporary relief

There are various theories as to the action of x ray and radioactive substances on the leukemic cells and therapy is based on the view taken by the operator Those who consider that irradiation causes some chemical change in the cell causing it to become necrotic and die give treatments by multiple exposures to the radioactive source They recognize some cells or stages in the growth of cells as radiosensitive e g myelocytes metamyelocytes young and old neutrophiles small lymphocytes and others which are radioresistant e g blast cells In giving repeated exposures over long periods of time it is assumed that blast cells which presumably are uninjured will mature to a stage in which they will be radiosensitive and thus be killed The period between the day of exposure to the radioactive source and the death of the cell is the latent period

A second view i that irradiation stimulates cells to advance to the next biological step in their development [1 15] Primitive blasts are made to divide faster and produce more blasts while the so called radiosensitive stages are made to mature to adult forms in which stage they die of senility The latent period between the time of exposure and the therapeutic result is according to this view the time for the cell to develop through the various stages to maturity and death This would vary with the normal life period of the type of cell a few hours or days for lymphocytes several days for neutrophiles and years for nerve or muscle cells The latter types would seem to be radioresistant then because one would have to wait years until their life span was completed Blasts seem radio resistant because they do not die after x ray exposure When a leukemic patient goes through the course of his disease blasts increase in number until practically all of the leukocytes in the blood forming organs and the blood are in the blast stage This leads to the statement that after many treatments the leukemia becomes radioresistant As long as the bulk of the cells are much more mature than blasts response to irradiation is therapeutically measurable by a decrease in the peripheral leukocyte count

duration than the myelogenous or lymphatic groups Osgood[147] calculated the average of 104 cases from the literature as five and one fourth months The shortest duration was ten days and the longest four years In our series the duration was somewhat longer for the chronic types averaging about 2 5 years

In all types of leukemia individuals living much longer than the average are encountered including cases surviving for from 10 to 17 or more years after the diagnosis was made There appear to be marked differences in the rapidity of the development in different cases and some live a long time without specific treatment whereas others die soon in spite of it As a whole the prognosis for a useful and possibly longer life is better now than it was 10 or 20 years ago

Death in chronic leukemia may result from hemorrhage infection pneumonia or cachexia In some there is gradual sinking terminating in death without an evident acute episode to indicate why the patient died at that particular time

Terminally there may be leukemic dyspnea characterized by marked air hunger with deep loud inspiration and expiration It is presumably related to blocking of the pulmonary capillaries with large leukemic cells

Prophylaxis

Because of suggestions as to the relation of chronic sepsis to leukemia probably it is well to remove foci of infection in individuals suffering from leukemia in the early stages although no curative results may be expected Roentgenotherapy is not prophylactic and it is useful only when there is a very specific indication for treatment Special preventive methods before operation are outlined under Operations

There appears to be no danger of contracting the disease from another person and the hereditary factor in human beings is practically negligible

Treatment

As soon as the diagnosis of leukemia is made the problem of treatment should be considered The data to be considered are (a) type of leukemia acute or chronic (b) estimate of the basal metabolic rate by laboratory study, if possible or by evaluation of pulse rate tendency to loss of weight perspiration, insomnia, irritability nervousness (c) degree of anemia is it progressive? (d) height of leukocyte count, (e) degree of maturity of the cells are there many blasts? (f) previous treatment, (g) tendency to bleed (h) the general symptomatology

A high leukocyte count alone is not an indication for x ray therapy and greater weight should be given to evidences of a high basal metabolic rate Progressive anemia or falling platelet count are indications for treatment The

higher the number of blasts the less the desirability of using x ray therapy and when the percentage is over 10 it is not wise to use this type of therapy unless immediate symptomatic relief is imperative

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There are various theories as to the action of x ray and radioactive substances on the leukemic cells and therapy is based on the view taken by the operator Those who consider that irradiation causes some chemical change in the cell causing it to become necrotic and die give treatments by multiple exposures to the radioactive source They recognize some cells or stages in the growth of cells as radiosensitive e g myelocytes metamyelocytes young and old neutrophiles small lymphocytes and others which are radioresistant e g blast cells In giving repeated exposures over long periods of time it is assumed that blast cells which presumably are uninjured will mature to a stage in which they will be radiosensitive and thus be killed The period between the day of exposure to the radioactive source and the death of the cell is the latent period

A second view i that irradiation stimulates cells to advance to the next biological step in their development [1] [1] Primitive blasts are made to divide faster and produce more blasts while the so called radiosensitive stages are made to mature to adult forms in which stage they die of enility The latent period between the time of exposure and the therapeutic result is according to this view the time for the cell to develop through the various stages to maturity and death This would vary with the normal life period of the type of cell a few hours or days for lymphocytes several days for neutrophiles and years for nerve or muscle cells The latter types would seem to be radioresistant then because one would have to wait years until their life span was completed Blasts seem radio resistant because they do not die after x ray exposure When a leukemic patient goes through the course of his disease blasts increase in number until practically all of the leukocytes in the blood forming organs and the blood are in the blast stage This leads to the statement that after many treatments the leukemia becomes radioresistant As long as the bulk of the cells are much more mature than blasts response to irradiation is therapeutically measurable by a decrease in the peripheral leukocyte count

Depending on which view one takes, one would expose the patient many or few times to the x ray machine According to the first theory the more exposures the more blast cells are affected, as they have time to mature to radiosensitive forms According to the second theory as few exposures as possible are given, because every exposure while reducing the number of mature and relatively mature cells also increases the number of blast cells in the internal organs and, therefore hastens the time when blast cells predominate

From a review of the effects of different types of treatment on 1 000 cases over a period of years, the author favors the second theory, i e that irradiation stimulates cells to advance to the next biological step in their development and the treatment based on it It must be remembered, however, that excellent results may be obtained with many different modes of application of treatment in the hands of experienced x ray technicians Some patients appear to survive in spite of poor treatment whereas many have reached the blast stage earlier than otherwise they would have because of too much or too frequent irradiation

Monocytes are not reduced in number as rapidly as other types of leukocytes after x ray therapy They may be more radioresistant or they may have a rather long period of adult life They are sensitive to arsenic

At the present time there appears to be no cure for leukemia although some very long and asymptomatic remissions have been produced Some patients have shown blood pictures suggestive of leukemia but have recovered In these cases the question of a wrong diagnosis always has to be considered Symptomatic treatment of the disease enables many patients to live comfortable and useful lives until the terminal picture develops [1, 1, 6]

General Treatment

Rest and Exercise — As the disease progresses, ease of fatigue becomes the outstanding symptom While the exact cause of this is not clear several factors contribute to its production Anemia with defective tissue oxidation and myocardial fatigue cause symptoms in proportion to the cardiac insufficiency There is usually an elevated basal metabolic rate associated with nervousness and excessive activity Fever and drenching perspiration deplete the patient s strength Lessened room for lung expansion with lowered vital capacity, crowding of the abdominal organs from enlarged spleen liver and lymph nodes and enlarged mediastinal lymph nodes handicap the patient and limit his activities

These factors serve to drain the patient s energy and require rest If the period of voluntary apnoea i e holding the breath as long as possible without previously having taken a deep breath is less than fifteen seconds it is wise to keep the patient in bed When the patient does not become too dyspneic on the

necessary exertion of walking a short distance he may be allowed toilet privileges

With improvement in the blood and physical condition normal activities should be resumed and the patient may engage in his normal occupation The physician must check the patient s blood at frequent intervals to note evidences of relapse A sharp persistent pain in the splenic region may indicate a splenic infarct hemorrhage or perisplenitis and then bed rest is indicated When there is a hemorrhagic tendency exercise must be restricted and in the presence of gross hemorrhage especially gastrointestinal strict bed rest must be enforced When there is evidence of leukemic gastric ulcers pleural effusion or ascites activity must be restricted

Diet — So far no special diet has been found which influences the course of the disease A normal nutritious diet should be outlined and a study of the patient s food habits should be made to see if there is any gross deficiency The high basal metabolic rate and fever require an adequate and easily available carbohydrate intake and a sufficient amount of protein with each meal to supply carbohydrate equivalent during the hours after meals when the blood sugar begins to fall

It may be necessary to prescribe six or more small meals a day instead of the three ordinary meals in the hope of reducing the feeling of fulness after meals especially when the enlarged spleen crowds the abdominal viscera

After roentgen ray therapy there may be loss of appetite severe nausea and vomiting The patients lose weight after each series of x ray treatments Before and during the x ray treatments soluble carbohydrates should be increased with a reduction of solid foods During this period the vitamins should be increased and especially the B complex in concentrated form should be given

General Surroundings — At present there appears to be no climatic influence in alleviating the disease One group of authors noted that it was easier to control the blood of a patient with chronic myelogenous leukemia in the summer than at other times In this patient ultraviolet light from artificial sources was of no therapeutic value

Irritability associated with the high basal metabolic rate requires sympathetic handling on the part of nurses and relatives

Roentgen ray Therapy

Indications — Roentgen ray therapy should not be prescribed just because the patient has leukemia There are several specific indications and several contraindications It is necessary to take into account (a) the white blood cell count (b) the degree of maturity or immaturity of the cells (c) the type of

the white blood cells (d) the degree of anemia, (e) the general symptomatology and (f) the elevation of the basal metabolic rate and the symptoms associated with it such as loss of weight perspiration, nervousness, rapid pulse

A high white blood cell count alone does not call for immediate irradiation, but more weight should be given to the associated basal metabolic rate When the metabolic rate is high irradiation treatment may be valuable The more severe the anemia the greater is the importance of treatment Roentgen ray irradiation is contraindicated when the majority of the cells are blasts and one should hesitate about treating, if blasts constitute 10 per cent of the cell types

It is necessary to give roentgen ray therapy when there is a tendency to bleed especially when the leukocyte count is high the cells fairly mature and an operative procedure as extraction of a tooth is necessary When the leukocyte count is less than 6 000 per cu mm as in aleukemic leukemia it is wise to avoid x ray therapy although it is not always contraindicated When one knows that the marrow is crowded with fairly mature cells x ray treatment may be given *Some recommend radium under these conditions*

After successful irradiation therapy there is (a) reduction of basal metabolic rate (b) cessation of fever (c) reduction in leukocyte count to a safe level not necessarily normal, as some patients feel perfectly comfortable with a leukocyte count of 20 000 to 30 000 per cu mm (e) reduction of the anemia (f) improvement in the tendency to bleed and (g) reduction in size of the spleen and the enlarged lymph nodes

Every patient presents a separate problem and requires careful study before irradiation therapy is given The blood should be examined at least every four weeks throughout the course of the disease to note evidences of relapse, progressive anemia platelet deficiency and progressive immaturity of the cells

TECHNIC — Each operator devises a technic of irradiation which appears to give the best results with his given apparatus There are many methods in general practice Exposure may be made over the spleen region anteriorly or posteriorly the mediastinum the long bones, the peripheral lymph node areas or the whole body Some irradiate the kidney region or the spinal column paravertebral ganglia For practical purposes exposure over the spleen region appears to be satisfactory and is the plan advocated by the author of this chapter

A sample technic may be illustrated by the following Chronic myelogenous leukemia Exposure factors 200 Kv p (Villard circuit), (175 Kv constant potential equivalent) 25 Ma filter 0 5 mm copper + 1 0 mm Aluminum focal skin distance = 50 cm H V L = 1 0 mm copper Approximately 50 r/min intensity *Technic* Anterior posterior and lateral ports are used over the spleen These vary in size from 100 to 400 sq cm the usual sized port being about 200 sq cm To one port per day 100, 150 or 200 r are delivered The selection

depends to a certain extent upon the size of the spleen the severity of the disease the level of the white blood cell count the degree of maturity of the cells the number of previous irradiations and the general condition of the patient Similar treatment is given to the other ports and may be repeated to all of the ports usually not exceeding a total of six treatments depending upon the response of the blood count and of the patient to the irradiation Most patients receive three exposures before it seems wise to discontinue therapy One guide used in this determination is to discontinue treatment of a patient if the white blood cell count falls rapidly to below 100 000 although this is not the only criterion Both the speed of the fall as well as the cell number must be taken into account

Chronic lymphatic leukemia —The exposure factors are the same as just given for chronic myelogenous leukemia The spleen and lymph nodes are radiated if they appear to be involved in the leukemic process The ribs are radiated occasionally if gross invasion of the bone marrow is evident from low red blood cell count low hemoglobin percentage low platelet count and nucleated red blood cells with comparatively few reticulocytes in the peripheral blood Doses ranging from 100 to 200 r per port are used over multiple ports Lymphatic leukemia may be treated until the white blood cell count is as low as 50 000 per cu mm

The method of cross fire results in the optimum penetration of rays into the deep seated organs with a minimum of injury to the skin The white blood cell count continues to fall after irradiation is stopped and the effects may be noted for as long as six weeks

Roentgen ray irradiation should be repeated only when the symptoms indicate that it is necessary and not in a routine fashion at regular weekly or monthly intervals Irradiation treatment is not prophylactic and routine doses at regular intervals may hasten the appearance of the blast radioresistant stage

Irradiation of the Kidneys —Some operators irradiate the kidney region with small doses preliminary to the general irradiation to produce better renal function[1] As a rule however this is not necessary

TOTAL IRRADIATION (*Continuous Irradiation Teleroentgenotherapy*) —Irradiation for long periods with the tube from 1 to 7 4 meters from the body have been recommended by some authors covering periods of four days to five weeks The reports have varied from excellent results even in radio and arsenic resistant cases to the most adverse comments, such as severe inhibition of erythropoiesis more severe x ray sickness than with the other methods and unpleasantness of the multiple and prolonged treatments from the point of view of the patients

The purpose of this method is to treat the entire body in several treatment with small amounts of radiation These treatments are given at a target skin

distance of 100 to 150 cm with 200 K V and an equivalent of 1 to 2 mm copper filtration The single dose consists of 25 to 35 r, maximum 50 r, and is applied twice weekly in the average case Depending upon the severity of symptoms the treatment may have to be repeated four to six or even eight times in order to get desired results

No cone is used in these treatments but the exposure may be limited to the trunk or extremities

Roentgen ray Sickness

During and after x ray therapy the patient usually loses weight because of loss of appetite nausea and vomiting This may be relieved somewhat by the use of vitamin B complex glucose orange juice or intramuscular liver extract or thiamin The nausea disappears in from one to three days after the x ray therapy has been discontinued Nausea is less marked when small doses are used and in the method of spray therapy It is more marked when extensive treatment has been given over the abdomen The effect of the radiation therapy on the blood and marrow is not complete until about six weeks after treatment A regular well balanced diet is indicated as the patient resumes his normal activities following a course of x ray treatment

Radium Therapy

The end result of radium treatment is the same as with x ray therapy but the time of exposure is longer There are various forms of technics for administration of irradiation with radium That of Ordway[1] is as follows Screens or filters of lead two to three mm in thickness or of brass 1 2 mm may be used The applicator is wrapped in twenty five to thirty layers of gauze It must be protected by lead above as well as below The area of the spleen is marked out on a piece of overlying thin cotton cloth used to attach the adhesive strips holding the applicator without injuring the skin and this is divided into small squares 3 cm in diameter The radium applicator 2 cm x 2 cm containing 25 to 100 mgm of radium evenly distributed on the surface, is left in each position in the middle of the marked off squares for from four to six hours with the proper screening and gauze

If radium emanation radon is used 100 mc are applied in the same manner With smaller amounts of radium the time must be lengthened Treatment should be discontinued, if the white blood cell count falls to 25 000 to 30,000 per cu mm

Treatment with Other Radioactive Substances

Among the substances proposed for treatment of leukemia are thorium x[111] thorium emanation thorotrast and radioactivated phosphorus as sodium phosphate

Thorium x is not used extensively at present It can be given orally subcutaneously or intravenously in sterile physiological salt solution The radioactivity of the preparation must be determined before injection in terms of electrostatic units or the number of milligrams of radium bromide to which it is equivalent The dose is 500 electrostatic units equivalent to 0 18 mgm of radium bromide to 800 electrostatic units equivalent to 0 30 mgm of radium bromide The dose may be given at intervals of eight days with careful blood studies to control the frequency

Radioactivated sodium phosphate produced with the cyclotron and other activated salts which have a short life but can be given in large doses are now being studied[11 1 3 11 1]

Phosphorus is activated in a cyclotron and then is converted into dibasic sodium phosphate The dose by mouth is from 1 to 20 millicuries less than 3 grams of sodium phosphate taken in orange juice No laxatives are taken for a day before or a day after the medication Single intravenous doses vary from 0 1 to 3 millicuries less than 1 gram of sodium phosphate The sterilized solution is kept in vaccine bottles The initial dose may be small 0 1 to 0 3 millicuries and if it is well tolerated the larger doses may be given

The action is like that of x ray or radium in the reduction of the number of white blood cells and in the production of a symptomatic remission As with other methods of therapy the remissions may be short or long About fifty per cent of the substance is excreted in the urine during the first six days and some appears in the feces Most of the substance is eliminated in about six weeks After death the highest concentration of the radioactive phosphorus isotope P is found in the liver bone marrow ribs vertebral bodies sternum spleen lymph nodes testes and kidneys No morphological alterations have been noted in normal tissues

Because of the simplicity of administration and the practical absence of after effects of irradiation the method bids well to have distinct advantages over the present forms of radiation therapy Remissions of over two years duration have been reported in two patients with chronic myelogenous leukemia after the use of radioactive phosphorus The chief value lies in the treatment of chronic myelogenous and chronic lymphatic leukemia No therapeutic advantage has been found in patients with acute leukemia Unfortunately at this writing March 1943 it is not commercially available to practitioners

Blood Changes after Roentgen ray or Radium Therapy

The blood changes after irradiation may be summarized as follows

1 Within twenty four hours after the first application of x ray the total leukocyte count rises followed by a decrease during the following days

2 In chronic myelogenous leukemia successive peaks of increased number of myeloblasts myelocytes metamyelocytes and young and old polymorphonuclear leukocytes appear in the blood stream in the order named after irradiation followed by a decrease in the more immature stages

3 During this period the basal metabolic rate rises, showing increased oxygen utilization

4 Chemical changes associated with cell growth are accentuated immediately after treatment is started There is an initial rise in the level of the total phosphorus content of the plasma and frequently a rise in the total phosphorus content of the corpuscles within twenty four hours after irradiation therapy Similar changes in the nitrogen and uric acid metabolism are noted

5 Studies of cells by supravital stains show an increase in neutral red granules i e older stage and a decrease in the number of Janus green granules, evidence of youth after irradiation[11]

6 The number of mitotic figures i e myeloblast stimulation increases in the bone marrow twelve to twenty four hours after irradiation[118]

7 The increase in age of leukocytes after irradiation is shown by short interval observations of the number of lobes as the criterion of age Kennedy and Grover[119] found that the number of leukocytes with one lobe reached its maximum *three and one quarter hours after irradiation of rabbits*, those with two lobes reached their maximum in one to two days with three lobes in four to five days with four lobes in six to seven days and with five lobes or more after this

Studies of the effects of irradiation show that (a) the decrease in number of cells in the peripheral circulation is progressive and takes some days or weeks (b) the process is an orderly one in which there are successive waves of maturity noted in the cells increase in myeloblasts myelocytes metamyelocytes polymorphonuclear neutrophiles lymphoblasts large lymphocytes small lymphocytes followed in about six to eight days in the myeloid series and in about four to five days in the lymphoid group with a small second peak of increased cell production (c) the cells undergo no new i e specific for x ray processes but appear to follow the normal growth sequence of the myeloid or lymphoid cells (d) similar effects follow blood transfusion arsenic benzol and amidopyrine and occasionally they appear spontaneously In patients who receive adequate irradiation therapy those whose cells in the peripheral circulation are predominantly myelocytes or older or small or medium lymphocytes respond well, whereas

those whose cells are myeloblasts or lymphoblasts or younger respond very poorly

Arsenic Therapy

Arsenic may be given in the form of Fowler s solution either by mouth or by intravenous injection If used after roentgen ray therapy the treatment should not be begun until the post irradiation decline of the leukocytes has reached its lowest point[1]

The dose may be started at 0 2 c c 3 minims in water three times a day after meals increasing one minim a day until the dose approaches 35 to 45 minims per day In practice it has been found more feasible to order 3 drops from a dropper held vertically three times a day The increase per day is one drop If toxic symptoms appear the dose should be reduced and then increased gradually The maintenance dose is the largest dose which the patient can tolerate The most common dose is 7 drops three times a day Some recommend 14 or 21 day cycles of arsenic interspersed with 7 to 21 day rest periods Toxic symptoms may show themselves as herpes zoster cirrhosis keratosis exfoliation polyneuritis erythema portal fibrosis ascites moist rales heard over the lungs chronic cough conjunctival and nasal congestion and gastrointestinal disorders Edema of the eyelids and face lacrimation loss of appetite vomiting restlessness and sleeplessness pigmentation diarrhea and fall in the number of red blood cells and hemoglobin content may be noted The milder symptoms disappear when the drug is withdrawn for from 2 to 5 days and then is resumed at a lower level

Arsenic is most useful in chronic myelogenous and monocytic leukemia less effective in chronic lymphatic leukemia It usually does not influence the acute blast forms of leukemia but in individual cases especially after a series of blood transfusions there may be a temporary improvement in the blood picture

Forkner s directions for the administration of Fowler s solution are as follows

1 Begin with doses of about 5 minims (0 3 c c) three times daily for two days preferably in orange juice immediately after or with meals On the third and fourth days give 6 minims three times daily and continue increasing in this manner to about 10 minims three times daily thereafter increasing by 1 minim per day until toxic symptoms are pronounced or until the leukocyte count approaches normal Thereafter omit medication for from two to five days and then decrease the dose from the maximum by 1 minim per day down to a maintenance dose of from 5 to 8 minims three times daily Continue this dosage indefinitely

2 The best results are obtained by the rapid and relentless administration

of the drug Patients, who take their medicine in a hit or miss fashion, do not respond well

"3 Do not decrease the dosage of Fowler s solution until the leukocyte count is near normal and then decrease gradually according to the above plan There is apparently no danger of producing an actual and permanent aplasia of the blood forming organs

4 Omission of the medicine for longer than one week is of no advantage and may eventually necessitate more medication than if continued in small doses

5 Disregard mild toxic symptoms

"6 Patients often believe that they cannot take Fowler s solution and will become nauseated and will vomit even when taking as little as 3 minims three times daily All of our patients, who have shown these symptoms, have been able to take the medicine well, if it is masked in orange juice or in some other vehicle

7 If a patient has diarrhea or vomiting and if he has taken only small amounts of Fowler s solution and the leukocyte count remains high, give by rectum in a few ounces of water twice the dose which he should be taking by mouth If for any reason the patient cannot take the medicine either by mouth or by rectum a solution of potassium arsenite 1 per cent arsenic trioxide, corresponding to the United States Pharmacopoeia January 1 1926 page 222 but with the omission of tincture of lavender may be prepared and given intravenously twice daily in about 20 c c of physiologic saline solution The total daily intravenous dose should be somewhat smaller than the calculated dose which the patient ordinarily would take by mouth"

Blood Transfusions in Treatment

Transfusion of blood may give considerable symptomatic relief in all types of leukemia with an improvement in the blood picture both of the red and the white blood cells When there is marked anemia 500 c c of blood may be given at intervals of from twice a week to once every two weeks, depending on the height of the red blood cell count Transfusion of blood from one type of leukemia into another has not been of marked therapeutic value[2]"

Iodine in Treatment

Some patients with lymphatic leukemia obtain excellent symptomatic relief from symptoms of an elevated basal metabolic rate by the use of Lugol s solution Friedgood[1 4 1 5] used 1 0 c c, 15 minims of Lugol s solution two or three times a day for several weeks There may be a decrease in nervousness irritabil

itv sweating and insomnia in some patients, but others may show an exaggeration of their symptoms The treatment is not as effective in chronic myelogenous leukemia and some patients show no subjective relief There is no improvement in the blood picture in any of the patients

Splenectomy

Splenectomy may be considered in individual patients but as a rule little good is accomplished by removal of the spleen The liver may enlarge excessively and the handicap of an abdominal mass still is present Adhesions following extensive roentgenotherapy or perisplenitis associated with infarcts may make surgical removal extremely difficult

Thyroidectomy

Remissions both hematological and symptomatic, have been produced in leukemic patients having a high basal metabolic rate by thyroidectomy [6] The utilization of this therapy is extremely limited

Liver in Treatment

Liver and liver extract as well as ventriculin appear to be of no use in myelogenous or monocytic leukemia In chronic lymphatic leukemia maintenance of red blood cell level and hemoglobin content have been facilitated by having the patients take as near 225 grams, one half pound of cooked whole liver as possible daily or five or six times a week Liver extracts used in treating pernicious anemia are not effective

Iron in Treatment

As the red blood cells have no space in which they can grow when the marrow is crowded with leukemic cells iron is of little therapeutic value After the leukocyte count has been reduced by therapy iron may be prescribed if the color index is low

Extract of Bone Marrow in Treatment

A hydrochloric extract of fresh macerated beef ribs has been used by Cooke[1] 100 c c of the solution represents approximately one pound of original ground ribs of this solution 2 to 5 c c diluted several times with water are given slowly into a vein Remissions were produced in acute leukemia by this method when

combined with blood transfusions Fresh bone marrow has been advocated[1] , but no benefit in chronic myelogenous or chronic lymphogenous leukemia has been reported following the administration of large amounts of raw spleen bone marrow, liver or lymph nodes[48] or of desiccated mucosa of the stomach and small intestine, desiccated hog pancreas and mixtures of most of the fresh organs of newly born rabbits[1 8] or beef lymph nodes Beef duodenum, hog spleen and beef bone marrow by mouth or extracts given parenterally were not followed by hematological improvement[1 9]

Benzol and Other Substances in Treatment

Benzol was used formerly to reduce the white blood cell count but is not used extensively at present It is rather difficult to control, and the red blood cell tissue is injured with resulting anemia Among the substances which have been reported as influencing the course of leukemia or as having been tried experimentally but which have not received wide acceptance at present, are phosphorus naphthalin tetrachloride potassium antimonyl tartarate, sulphur and sulphur compounds oxygen ergot colchicine ergotamin tartarate, tuberculin, lead, Coley s toxin colloidal metals cinnamic acid quinine, amidopyrine malarial inoculation leukotoxins and leukolysins, thyroxin, insulin, posterior lobe of the pituitary and vaccines

Vitamin C in Treatment

Because of the spongy appearance of the gums with bleeding in some patients and its resemblance to scurvy the use of vitamin C is suggested Eufinger and Gaehtgens[130] reported that they were able to lower the leukocyte count of a patient with chronic myelogenous leukemia to normal by the injection of 2 000 mgm of ascorbic acid This observation however, has not received wide confirmation other authors[131 13] reporting negative results Ascorbic acid, not the sodium salt, stimulates leukocyte formation when given intravenously Heinild and Shødt[133] recommended cevitamic acid in acute myeloblastic and chronic lymphatic leukemia claiming for it decrease in leukocyte count and cessation of hemorrhage

Treatment of Special Symptoms

Cough — The hacking non productive cough in leukemia is due to irritation of the bronchi from pressure of enlarged lymph nodes or to filling of the capillaries with large leukemic cells Ordinary cough medicines are not effective, but roentgenotherapy causes rapid improvement In the interval between treat

ments codeine sulphate 0 032 grams (½ grain) and tincture of belladonna 5 to 10 minims may be given every three or four hours Heat moist or dry applied to the upper part of the chest over the sternum may give temporary relief

Pain in leukemia is caused by pressure from enlarged lymph nodes by periostitis perisplenitis or pleurisy, and it may be local or referred to a distant region Roentgenotherapy applied over the source of the pain often gives dramatic relief within a matter of hours or a day or two This is especially true for pains in the lumbar region and the legs Acetylsalicylic acid, 0 3 to 0 6 grams (5 to 10 grains), combined with codeine sulphate 0 032 to 0 065 grams (½ to 1 grain) every four hours may be given when necessary

Acute Pain in Splenic Region — Hemorrhage or splenic infarct may produce acute pain in the region of the spleen The patient is kept in bed and heat or cold is applied over the region of the pain depending on which gives the most relief There is no specific treatment and recovery usually follows a period of rest with codeine or morphine to relieve the pain Fever may be present and may be controlled with acetylsalicylic acid 0 3 grams (5 grains) every three hours

Tinnitus — Invasion of the tissues of the ear and congestion of the capillaries with leukemic cells give rise to a roaring sensation in the ears or head and often varying degrees of deafness Roentgenotherapy applied to reduce the general blood count gives subjective relief or improvement

Priapism — Priapism may appear for short or long periods (weeks) There is pain and difficulty in urination The symptom may disappear spontaneously X ray therapy appears most effective and should be directed over the pelvis and lumbar region Gangrene is a rare complication Surgical drainage or removal of thrombi from the corpus cavernosa may be necessary

Treatment of Aleukemic or Subleukemic Forms

Fricke and Watkins [24] recommend the use of radium instead of x ray when treatment is needed urgently and the leukocyte count is low The treatment is given over the splenic area One 50 mgm tube or at most two well filtered with lead are used at a distance of one inch (2 5 cm) from the skin for a time varying from eight to twelve hours depending on the leukocyte count the size of the spleen and the general condition of the patient Treatments are stopped or continued according to the results of the daily blood counts A decrease in the leukocyte count or an increase in the degree of anemia suggests a discontinuance of the irradiation As a rule there is an increase in the red blood cell count in the cases reported

Blood transfusion is helpful in these cases and may be given at intervals of one or two weeks Cevitamic acid 200 mgm intravenously daily may be tried

Fowler s solution may be tried cautiously and in small doses, 3 to 5 drops, three times a day, after meals, when it is known that the marrow is crowded with fairly mature cells

Treatment of Complications

Hemorrhage in Leukemia — Hemorrhage follows operative procedures, and even the removal of a tooth may be followed by serious and uncontrolled blood loss In the acute types and in the blast stage of chronic leukemia and in lymphatic leukemia there is a deficit of blood platelets while in the chronic myelogenous form the failure of the clot to retract is a mechanical feature secondary to the large number of leukocytes

In acute leukemia temporary relief may follow blood transfusion Fer de lance or Russell s viper snake venom in the diluted commercial form may be used locally This appears to be effective in all types of leukemia and is useful in bleeding around the gums or from tooth sockets In chronic lymphatic and myelogenous leukemia and to a less extent in monocytic leukemia roentgen ray therapy must be used and the bleeding decreases with the fall in the leukocyte count Some reports indicate that ascorbic acid, 200 mgm intravenously daily, may have some value in the control of the bleeding [8] Placental extract has been recommended[13] Pectin 1 gram (15 grains), in capsules may be given three times a day one half hour before meals Hemorrhage from the gums and uterus may be a serious terminal symptom

Fatigue — For the symptomatic treatment of the ease of fatigue no simple medication is effective The symptom disappears or decreases when a remission has been established with radiation or other therapy Among the drugs which have given suggestive results in individual patients are benzedrine sulphate 10 mgm ($\frac{1}{6}$ grain) once daily caffeine citrate 0 13 grams (2 grains), two or three times a day, alone or combined with acetylsalicylic acid 0 3 grams (5 grains) ephedrine sulphate, 25 mgm ($\frac{3}{8}$ grain) one to three times a day atropine sulphate, 0 4 mgm ($\frac{1}{150}$ grain) three times a day or tincture of belladonna 0 6 c c (10 minims), three times a day

Gastric Ulcer — The ulceration of the lining of the stomach is a very late symptom and may not be recognized during life Ordinary gastric ulcer therapy may relieve symptoms but appears to have no curative effect If the diagnosis is made before the blast stage of the leukocytes supervenes roentgenotherapy may be used otherwise it is contraindicated Atropine may be used to relieve discomfort or pain

Mouth Lesions — Ulcerative and bleeding stomatitis ulcerative pharyngitis spongy and bleeding gums usually are serious symptoms in leukemia especially in the acute leukemias For the bleeding fer de lance or Russell s viper snake

venom coagulen fibrogen or epinephrin may be applied on cotton or gauze pledgets with pressure of the gums Monsel s solution may be of value occasionally for individual bleeding spots if used very cautiously An empirical preparation which has helped some patients is tincture of kino 10 0 c c (2½ drachms), tincture of myrrh q.s 30 0 c c (1 ounce) This is applied directly to the gums Solutions containing sulfathiazole in su pension may be used as sprays

Mouth washes serve mostly to take away unpleasant tastes and odors but not much can be hoped for in the way of disinfection Boric acid powder suspended in water or peppermint water may be used as a mouth wash or irrigating solution The patient may dissolve peppermint wintergreen or clove candies life saver candies or similar products in his mouth The oil of cloves has slight antiseptic and anesthetic properties Zinc peroxide medicinal grade sterilized one part may be suspended in water four parts and used as a wash one mouthful every three or four hours[1] For an alkaline solution liquor alkalinus antisepticus N F may be used Alkaline solutions may help to dissolve mucus, but ometimes there is danger of dissolving soft clots and reopening bleeding areas Brushing of the teeth must be avoided Hydrogen peroxide, in dilute solution may be used

Extraction of teeth of leukemic patients is dangerous as uncontrollable hemorrhage may follow Necrosis of the tissues may develop and hasten the terminal picture Teeth may be pulled after a remission has been induced by radiation or arsenic and the leukocyte and platelet count are not grossly abnormal If a tooth has been pulled when the leukocyte count is high and there is much bleeding roentgenotherapy should be started A blood transfusion may be of help in some patients

Herpes — Herpes occasionally hemorrhagic may appear around the mouth or on the trunk Its occurrence is not uncommon in leukemia For the pruritus lotio calomine compound N F containing phenol may be painted over the itching area For vesicles ammoniated mercury with 2 per cent phenol or carbolated vaselin may be applied Picric acid saturated aqueous solution may be painted over the lesions If the pain is marked sodium iodide 1 gram (15 grains) in sterile aqueous solution may be given intravenously This may be repeated on the following day if the pain persists Roentgenotherapy over the spinal roots has been effective in some cases

Operations — If time permits roentgenotherapy should be used before operation and the number of leukocytes reduced to below 25 000 if possible Blood transfusion 500 c c may be given before the operation and after if necessary The greatest dangers are hemorrhage and failure to heal with the development of necrosis and gangrene In an emergency operation transfusion must be given be

fore and after the operation Unusual care must be used to close bleeding vessels and to block capillary areas Snake venom (fer de lance or Russell s viper), fibrogen or, when the platelets are decreased in number, coagulen may be applied to oozing areas

Coughing characteristic of leukemia may complicate convalescence, and operative scars may open or stretch with the development of hernias

Pregnancy and Leukemia — *While it is wise for a leukemic individual to* avoid pregnancy it is not necessary to terminate the course prematurely if the pregnancy has started Infants born of leukemic mothers are normal and show no signs of the disease The question of operative interference may be considered if the spleen is extremely enlarged and will not allow room in the abdomen for the expanding uterus There is more danger after abortion than if the pregnancy is allowed to run its course If intensive x ray therapy must be given during pregnancy there is theoretical danger of malformation or other injury to the child While some infants have been born without apparent injury after roentgen treatment of the mother[1, 7] Rolleston[138] found that of 75 infants born of non leukemic mothers who had been irradiated during pregnancy, 18 were microcephalic idiots and only 19 were perfectly healthy The pregnancy or the puerperium does not appear to influence the course of the disease in chronic leukemia but death usually is hastened in acute leukemia[139, 140, 141, 142, 143, 144, 145]

Prevention of pregnancy may be considered in leukemic women Castration by roentgenotherapy may be accomplished during intensive treatment, but this is not always permanent In two such cases pregnancy resulted in the production of normal children although abnormal children have been born to others

Skin Lesions and Pruritus — The indurative skin lesions may be treated with x ray and frequently they respond by decreasing in size Purpuric lesions require no treatment Some patients develop severe generalized pruritus most commonly in chronic lymphatic leukemia This is a difficult symptom to treat and local applications of antipruritic medication usually is ineffective A few patients have had relief from superficial x ray therapy others after taking tincture of belladonna five drops three or four times a day

Convalescence

Effective x ray therapy does not prolong the patient s life materially, although the life of individual patients no doubt is lengthened in patients with the respiratory channel blocked by pressure from enlarged mediastinal lymph nodes In general, x ray treatment makes the patient more comfortable and prevents or delays the anemia and hemorrhagic stage reduces the size of enlarged lymph nodes or the spleen and reduces the basal metabolic rate

Less Common Types of Leukemia and Leukemia-like Conditions

Acute or Blast Leukemia

Acute leukemia is a rapidly evolving form of the disease starting with symptoms of infection such as pharyngitis tonsillitis ulcerative stomatitis or upper respiratory infections and developing a leukoblastic blood picture a hemorrhagic tendency fever and a fatal termination

Symptomatology — The *onset* may be acute and fulminating or it may be insidious suggesting failure to regain normal health after an attack of flu or upper respiratory infection The disease may be noticed for the first time because of a bleeding tendency such as hemorrhages from the mucous membranes purpura severe hemorrhage after tonsillectomy or the extraction of a tooth

The disease is marked by extreme prostration dizziness weakness rapid pulse rate high fever headache varying degrees of enlargement of the lymph nodes spleen and liver and gastrointestinal disturbances as anorexia vomiting diarrhea and blood in the stools Blurring of vision from retinal hemorrhages is common and ear lesions may be noted There may be pericarditis with effusion There may be tenderness over the bones with aching associated with symptoms of acute arthritis or periostitis There may be neurological and mental symptoms as coma twitching and convulsions associated with hemorrhage or infiltration in the nervous system Severe coughing with hemoptysis may be a feature Bronchitis or pneumonia with atypical symptoms because of the lack of neutrophiles may be present

Menorrhagia may be severe and prolonged Hematuria is noted in some patients and there may be frequency of urination or swollen testes Swelling of the salivary glands dysphagia and dysarthria are noted in some patients[14]

At autopsy there is extensive replacement of the bone marrow with blasts and change in the architecture of the spleen and lymph nodes from leukoblastic transformation Extensive hemorrhages may be noted on all serous surfaces and in all the organs The average weight of the spleen in acute lymphatic leukemia is 693 5 grams and in acute myelogenous leukemia 482 2 grams[14]

Age and Sex Incidence — While this type of leukemia is more common in early life than later cases have been encountered at any age Statistical analysis shows three peaks in the age distribution curve one at the age of five (5 to 10 year period) one at 35 years (15 to 45 year period) and a third peak at 50 years (45 to 65 year period) In Warren's [0] studies the disease was twice as frequent in males as in females However, in the age group between 45 and 50 years the disease was three times more frequent in females than in males presumably associated with the age of menopause

Course —The manifestations and course of the disease vary considerably in different patients The types have been characterized as asthenic and febrile agranulocytic, hemorrhagic, typhoid neoplastic, comatose and typical[1] There may be marked symptoms of an elevated basal metabolic rate, nervousness, irritability and profuse perspiration

Blood Picture —The blood picture shows a wide range of variations There may be leukopenia at some time, occasionally persisting to the end but in most cases a marked leukocytosis is noted In the myelogenous type leukocyte counts of from 15 000 to 60 000 per cu mm are most common with a few patients having a count of 100 000 or more In the lymphatic variety higher counts are more common and the number may reach 500 000 per cu mm In the monocytic type leukocyte counts varying between 15,000 and 45,000 per cu mm are most common reaching sometimes however, up to at least 400,000 per cu mm

The predominant white blood cell when the disease is fully developed is in the blast stage The myeloblasts and monocyte blasts may be accompanied by some oxidase positive cells, while the lymphoblast group is oxidase negative In some cases it is extremely difficult to identify the type and they are grouped under the name hemocytoblastic Some of the myeloblasts and monocyte blasts may show Auer s bodies, red staining rods in the cytoplasm

In the beginning the blood may show very few immature cells especially if the course is slow and there is leukopenia Gradually the blasts constitute about 85 to 95 per cent of the cells in the peripheral blood as well as in the blood forming organs There may be many atypical forms, suggesting abnormality in production

Anemia appears more or less rapidly in practically all of the patients It may be very severe with less than 1,000,000 per cu mm but with a color index around 1 With the progressive hemorrhage an iron deficiency may become evident in the cases which run a long course The red blood cells may be large and many are distorted Many nucleated red blood cells and reticulocytes appear at times but often the picture is that of aplastic anemia with but little evidence of regeneration

The platelets are markedly reduced in number, and this with the marked capillary fragility, positive tourniquet test forms the basis of the hemorrhagic tendency The coagulation time may be normal or prolonged with little or no clot retraction

Prognosis and Duration —While the disease is extremely serious remissions have been produced in several patients The most common duration from the first symptom to death is 4 weeks Most of the patients, 84 per cent, die in 8 weeks or less Some may live 6 months or longer, and these have been called subacute With the present use of multiple transfusions and the avoidance of

x ray therapy the average duration of the patient s life is longer than that of an earlier period

Pregnancy is a serious complication and the disease may be noted for the first time after the pregnancy has begun Abortion may take place spontaneously Death usually follows natural or induced termination of pregnancy

Death may be accompanied by hemorrhagic depletion hemorrhages into vital areas or infection as pneumonia Recently however a patient with acute monocytic leukemia went through an attack of lobar pneumonia which however remained unresolved Death followed some weeks later with a hemorrhagic episode

Differential Diagnosis —At present the diagnosis of the type of acute leukemia is an academic matter as the treatment and prognosis are not materially different Forkner[4] described a peculiar diffuse swelling of the mucous membranes of the mouth particularly the gums with ulceration and necrosis as characteristic of acute monocytic leukemia There is diffuse cellulitis about the lesions causing swelling and pain and signs of acute inflammation extending into the deeper tissues of the face

Differential points in the degree of enlargement of the spleen lymph nodes liver and histological and chemical reactions of the blood cells have been pointed out as characteristic of each group but are not always helpful in individual cases as the range of variation is so great

Acute leukemia may be confused with a number of diseases until the blood picture becomes diagnostic or until the diagnosis is made by examination of sternal puncture fluid showing predominance of blasts and suppression of other cells Among the diseases which may simulate some stage of acute leukemia are aplastic anemia agranulocytosis thrombocytopenic purpura Vincent s angina diphtheria scarlet fever, acute tonsillitis infectious mononucleosis sepsis miliary tuberculosis miliary carcinomatosis of the bone marrow and acute articular rheumatism

In infectious mononucleosis the sheep cell agglutination test heterophile agglutination may be positive in dilutions considerably above 1 60 whereas it is not positive in acute leukemia

Treatment —X ray therapy appears to increase the rapidity of the process and hasten death A few patients however have been reported as showing improvement after irradiation therapy The results so far with radioactive phosphorus have not been encouraging

In the beginning symptomatic improvement may follow repeated blood transfusions Later a stage is reached when there appears to be no elevation in the red blood cell count after transfusion and the prognosis becomes worse

In two patients who developed prolonged remissions bone marrow was as

pirated from normal, compatible donors and injected into the patients sternum This was given once or twice weekly, 4 to 5 c c at a time It was felt that ascorbic acid 200 mgm intravenously daily was followed by symptomatic improvement These patients received many blood transfusions at weekly intervals Fowler s solution may be used guardedly studying the effect of small doses first 3 to 5 drops three times a day in water after meals

Loss of appetite may be marked and the problem of feeding is difficult In some patients the nausea appears to be less marked after the use of 5 to 10 drops of tincture of belladonna three times a day one half to one hour before meals

In some patients coughing often followed by vomiting may be a terribly distressing feature The usual cough medicines including codeine may be used but may be ineffective Relief has been obtained in some instances from the application of heat a hot water bag electric pad or moist compresses, over the upper part of the chest anteriorly

Because of the weakness and severity of the symptoms most of the course of the disease may be spent in bed The problem of delaying or preventing bed sores is important As a rule it is necessary to use enemas frequently to induce bowel movements A simple soap suds enema may be used but may not be effective Some good results have been obtained from an enema composed of 120 to 240 c c (4 to 8 ounces) of mineral oil with 4 to 30 c c (1 drachm to 1 ounce) of castor oil thoroughly mixed and held as long as necessary At times it may be retained over night For distention, pituitrin or physostigmine may be used

Some improvement in the bleeding tendency may be obtained by giving 1 gm three 5 grain capsules of pectin powder, three or four times a day at least one half to one hour before food is taken In some this stops minor hemorrhages such as bleeding around the gums It is usually ineffective in the very advanced cases In one recent case the blood shortly before death, after the use of pectin, venous blood in a 1 cm diameter test tube clotted in less than one minute but clinical bleeding from gums and uterus was not stopped

For the mouth lesions the treatment is the same as given under chronic leukemia Local bleeding may respond to applications of fer de lance or Russell s viper snake venom in the dilute form The oxygen tent sometimes gives considerable relief when breathing is difficult

Chloroma Chloroleukemia

Chloroma is a rare condition in which tumor nodules appear in lymph nodes the orbit or any of the bones The nodules may develop during the course of leukemia or a leukemic picture may develop later The cell types in the tumors may be myelogenous, monocytic or lymphatic and the changes in the organs may

be characteristic of these types of leukemia A curious but inconstant feature is the olive greenish cast of the freshly cut nodes whence the name chloroma The exact nature of the pigment is not known The color tends to fade on exposure to the air Sometimes the nodules themselves appear greenish[1, 54]

Except for the pressure symptoms of the chloromatous masses pain exophthalmos periostial infiltration and elevation and bone changes the symptomatology is like that of leukemia in many cases like acute leukemia The blood varies with the type and duration and frequently the picture is that of acute leukemia with predominance of blasts[1, 154]

While patients of all ages may be affected it is probably more common in children and young adults The course may be acute or fairly chronic The average duration is 5½ months with some patients surviving for 2½ years At least one recovery has been reported

As complications develop from invasion of bones by the chloromatous tissue fractures may occur from pressure on the eye exophthalmos evulsion of the lids and ulceration may result invasion of the ear may cause deafness The exophthalmos may be unilateral at first later bilateral with resulting blinding

The growths may respond to x ray or radium but in the acute types of leukemia the process may be accelerated It may be necessary to remove a badly ulcerated eye

Lymphosarcoma Cell Leukemia

The blood of patients with lymphosarcoma may become leukemic This condition has been called leukosarcoma by Sternberg and lymphosarcoma terminating in lymphatic leukemia[1, 1, 100] Flashman and Leopold [1] noted 107 cases of this type in the literature and described an additional case On the basis of a lymphosarcoma presumably terminating in lymphatic leukemia numerous speculations have been published concerning the relationship of these two conditions A careful cytological study of the cell types in this form of leukemia has shown however that the cells are not lymphocytes but lymphosarcoma cells so that the condition is a true lymphosarcoma cell leukemia

Incidence — In one of the published reports of 43 patients with known lymphosarcoma 15 developed a leukocytosis during the course of the disease This group comprised 10 males and 5 females The ages of the patients ranged from 6 to 70 years with a fairly even distribution in the intervening decades except in the decade between 21 and 30 years which included one-third of the patients[14] Warthin noted leukemic transformation in 9 cases of lymphosarcoma out of a group of 134 biopsies

The Lymphosarcoma Cell — The lymphosarcoma cell in the blood stream usually is mistaken for a lymphocyte There are certain differentiating features

however the most marked being the peculiar characteristics of the nucleolus Usually this is placed eccentrically and is single, very rarely multiple In the films made on cover glasses containing brilliant cresyl blue, later stained with Wright s stain the nucleolus stands out as a sky blue, round area, surrounded by a deep, blue black rim of chromatin, which is piled up around it In the true immature lymphocyte or lymphoblast under these conditions the nucleolus appears as a *light blue hole or area in the chromatin structure without the heavily staining rim* The nucleoli are more likely to be multiple in the immature lymphocytes or lymphoblasts than in the lymphosarcoma cell

The lymphosarcoma cell in films varies in size from 7 5 by 9 microns to 12 by 13 5 microns The nucleus in films usually is oval or oblong, occasionally egg shaped and thicker at one end Kidney shaped or notched forms are common in some specimens The stained chromatin is coarsely reticular and somewhat spongy in structure and the chromatin around the edge is thickened into a fairly definite nuclear wall differing in this respect from the monocyte The cytoplasm of the cell is sparse deeply basophilic, and with the brilliant cresyl blue and Wright s stain appears as a fine, blue lacework

In sections of fixed tissue the lymphosarcoma cell is large and round, resembling the lymphoblast in size and in the proportion of practically non granular cytoplasm The nucleus may be irregular in size and shape, some showing indentations or lobulation

Unlike mature lymphocytes these cells do not show motility although both types show evidence of phagocytosis[164] The mitochondria are dust like as compared to the large rods and spheres of the mature lymphocyte and the small spheres of the lymphatic leukemia cell Deep scarlet neutral red vacuoles one to ten are present at the periphery of the nucleus in the sarcoma cell, although they are absent in the leukemic cell and when present in the mature lymphocyte, they stain a rose red

The Blood — There appear to be two phases of the blood in patients with lymphosarcoma an aleukemic and a leukemic phase In the aleukemic phase the leukocyte count varies from 6 000 to 10 000 per cu mm with 30 to 40 per cent of what are called lymphocytes Many of these cells are not true lymphocytes *but lymphosarcoma cells* The percentage varies from *3 or 4 to 25* or 30 in this group In the leukemic phase the leukocyte count rapidly increases to from 25 000 to 156 000 per cu mm or higher As the count increases the bulk of the cells are lymphosarcoma cells, in some cases forming 98 per cent of the total

As the leukemic process progresses anemia becomes more marked the average red blood cell count being around 2 5 million per cu mm In some patients it reaches a much lower level, 0 8 to 1 0 million The color index most fre

quently is around 1 or slightly below The blood platelets are increased in number in the early stages but decrease in the late stages

Clinical Course — In most of the patients enlargement of lymph nodes is the first sign noted The first evidence of the disease may be enlarged cervical, inguinal or submaxillary mediastinal lymph nodes with cough dyspnea pleural effusion abdominal symptoms sore throat or weakness Symptoms in order of their frequency are weight loss with an average of 15 pounds fever bleeding causing petechiae hemoptysis hematuria epistaxis hematemesis gross bleeding from mucous membranes or retinal hemorrhages joint pains pulmonary and hilar lesions with x ray evidence pleural effusion dyspnea chest pain or cough allergic symptoms herpes skin lesions as toxic erythema and erythema multiforme bone lesions facial palsy diplopia and local edema Very slight albuminuria during some stage of the disease is common The spleen size varies from 15 to 23 cm with an average of 16 5 cm and is palpable in about 50 per cent of the patients At autopsy the weights vary from 490 to 700 grams

With the onset of the leukemic phase fever is common 100 to 105 F Terminally 104° to 107° F may be noted Lung involvement is not always shown on the x ray films although autopsy in some of the patients shows infiltration of the alveolar walls and of the perivascular and peribronchial tissue with lymphosarcoma cells This type of lesion is the most common type in patients dying in the leukemic state whereas in those who are aleukemic on the day of death the lungs are not always involved The degree of leukemia is more parallel to the lung involvement than to the degree of peripheral lymph node enlargement

The duration of the disease varies from 2 5 to 36+ months The duration of the leukemic phase varied from 2 days to 60 days in 11 patients in whom approximate data were available but one patient gave a history of a leukemic blood picture 94 000 per cu mm diagnosed as lymphatic leukemia for over 7 years This patient had a white blood cell count of 37 000 with 84 per cent lymphosarcoma cells 27 days before death The maximum count was 73 000 The average duration of the leukemic phase in all of the other patients was 26 days Nine out of 15 patients gave a history of one or more of the common childhood diseases

Lymphosarcoma and Pregnancy — One patient with lymphosarcoma showed a remission during a period of pregnancy The patient a 31 year old woman was studied first after she had cervical and axillary lymph node enlargement for 18 months Her blood count at that time was as follows red blood cell count 3 500 000 per cu mm white blood cell count 47 800 hemoglobin 9 4 grams per 100 c c, atypical lymphocytes 65 per cent blasts 0 5 per cent She became pregnant 6 months later and during the third month she returned to the clinic

for examination At that time her red blood cell count was 4,000 000 per cu mm, white blood cells 7 100 per cu mm hemoglobin 12 9 grams per 100 c c, polymorphonuclear neutrophiles 71 per cent, large lymphocytes 15 per cent, small lymphocytes 9 per cent monocytes 5 per cent The adenopathy had practically disappeared A perfectly normal child was born in due course of time and 8 months after this the patient s blood count still was normal, but lymphosarcoma cells were noted on the blood films About 9 months after this the patient returned in complete relapse with a red blood cell count of 800 000 per cu mm, white blood cells 4 00 hemoglobin 88 grams per 100 c c Lymphosarcoma cells 7 per cent and one blast were noted She received two blood transfusions and had another remission An examination 4 months later showed her red blood cells at a level of 3 600 000 per cu mm, white blood cells 6 100, hemoglobin 10 5 grams per 100 c c lymphocytes 59 per cent

Effect of Roentgen ray Irradiation —In 11 of 15 patients the leukemic phase started after x ray therapy in 2 no x ray therapy was given and in it is uncertain whether the patients had received x ray therapy before they reported to the hospital A decrease in the number of leukocytes followed x ray therapy during the leukemic phase in 8 patients with severe leukopenia 3 500, 1 800, and 350 per cu mm, developing in three patients In 5 patients there was a subsequent increase in number after the initial decrease There appeared to be two stages in the effect of x ray therapy, an initial decrease in the number of leukocytes followed by a marked and rapid increase Thus in one man with a leukocyte count of 50 000 per cu mm 96 per cent lymphosarcoma cells 2 800 r were given over 12 positions in 15 days On the last day the count was 53 000 per cu mm Two days dater the count was 156 000 per cu mm and the patient died In another patient the initial count was 10 500 leukocytes per cu mm On 5 successive days 150 r were given The leukocyte count fell to 5 500 per cu mm Then t rose gradually to 15 200 with 66 per cent lymphosarcoma cells 43 days later Three days before death which followed 2 weeks after this, the count was 92 000 with 85 per cent lymphosarcoma cells A third example is that of a patient with 7 800 leukocytes per cu mm, who received 1,200 r over a 5 day period at the close of the treatments the leukocyte count was 6 800 per cu mm An observation 41 days later showed that the count had increased to 50 000 per cu mm and 3 days later to 70,800 per cu mm This patient died within four weeks

Pathological Changes in the Organs —Autopsy studies of the organs of patients dying during the leukemic phase show transformation in varying degrees of all lymphoid tissue in the body into the lymphosarcoma type The lymphoid follicles of the intestine and colon as well as the tonsils show this change There is marked invasion of the bone marrow with subperiosteal extension, which al o

involves the surrounding tissues All of the organs may show perivascular or tissue infiltration with lymphosarcoma cells

The frequent occurrence of the leukemic state of lymphosarcoma after roentgen ray therapy is of interest in connection with the observations of Krebs Rask Nielsen and Wagner[14] on the production of a leukosarcomatosis aleukemic and leukemic, in white mice after irradiation They found that the leukemic phase developed late in the course of the disease and that as in the cases cited here the prognosis was bad

In view of the tendency of the lymphosarcoma cell to invade the tissues it is not surprising that some of the cells enter the blood stream However it appears that the number does not reach leukemic proportions until there is extensive growth in moving organs as the lungs This phenomenon is similar to that found in other types of leukemia

Eosinophilic Cell Leukemia

A number of patients with eosinophilic leukocytosis with or without splenomegaly have been encountered As a rule the eosinophiles in these conditions are predominantly mature with relatively few immature forms although atypical cells may be present Myeloblasts and nucleated red blood cells may appear in the blood stream and the crowding of the marrow may be reflected in varying degrees of anemia and thrombocytopenia

Most of the reported cases had leukocyte counts of from 15 000 to 75 000 per cu mm with a few reaching 275 000 or higher The percentage of eosinophiles varied from 30 to 90 per cent The cells vary in size many being larger than normal The eosinophile granules may be large and sparse The absolute number of lymphocytes monocytes and frequently neutrophiles is normal or there may be increases or decreases depending on the stage of the disease

The disease may run an acute or a chronic course The tissues show gross infiltration with eosinophiles occasionally in nodular form Charcot Leyden crystals may be found in the spleen and other organs rarely in the blood Eosinophiles may be found in the spinal fluid in increased numbers Death in most cases was associated with infection such as pneumonia or with progressive anemia [7]

The symptomatology is much like that of acute or chronic myelogenous leukemia Some patients show more involvement of the lymph nodes than in the myelogenous form The sex distribution males predominantly is as in the other forms of leukemia The hepatomegaly splenomegaly and purpura are not different from the other types

Differential Diagnosis — Marked eosinophilia may appear in trichinosis al

lergy as in asthma and hay fever Hodgkin s disease, neoplasms, many types of parasitic infection eosinophilic splenomegaly, eosinophilic pleurisy, angioneurotic edema certain skin lesions, following splenectomy and in periarteritis nodosa Eosinophilia is common in chronic myelogenous leukemia, frequently increased after irradiation therapy

At times it is quite difficult to distinguish between symptomatic eosinophilia and true leukemia, leading some to discredit the occurrence of the latter[168]

Treatment — Splenectomy has been advised but probably is not of lasting value The response to x ray may be good and a remission may be produced

Plasma Cell Leukemia Multiple Myeloma

In some patients with plasma cell multiple myeloma numerous plasma cells appear in the blood stream[169] At times rarely, the picture is that of a plasma cell leukemia[170, 171] In these no myelomata, however, may be evident in the bones[173]

The true plasma cell appears to be a normal constituent of lymphoid tissue, and this may be the primary focus in some individuals The lymph nodes, liver and spleen may be enlarged, and fever may be present The leukocyte count may increase to 30 000 or 60 000 per cu mm with from 5 to 75 per cent of various stages in the development of plasma cells The earliest stage is a type of blast with a round nucleus developing later into an oval eccentrically placed nucleus in a deeply basophilic cytoplasm According to some there are several types myeloid or lymphoid of plasmacytomas

Multiple myeloma occurs most frequently between the ages of 40 and 70, less commonly in younger individuals The incidence in males is twice that of females The bone tumors may be single or multiple The symptoms are those of pressure or disturbance in normal pressure balance and the site of the pain or neurological symptoms depends on the location of the tumors Bence Jones protein frequently is present in the urine Besides plasma cells 1 to 5 or more per cent immature bone marrow cells myelocytes nucleated red blood cells, may appear in the blood stream There may be a normal red blood cell count in the beginning but a marked anemia may develop especially if the blood becomes leukemic The platelets may become reduced in number[174, 175]

There may be marked autoagglutination and rouleau formation of the red blood cells There may be a marked increase in certain of the plasma proteins The tonsils, liver kidneys spleen bones bone marrow pancreas and lymph nodes usually show infiltration with plasma cells in the leukemic stages of the disease Tumor like deposits of amyloid may be found in or around the joints[177] The blood calcium may be increased in amount with normal or high values for

serum phosphorus[178] The duration of reported cases has been from 3 weeks to 3 years Death may follow pathological fracture or infection, pneumonia Hemorrhage a symptom during the course of the disease may be a marked terminal factor Alleviation of pain and temporary remissions may follow x ray therapy Blood transfusion may be of symptomatic value

Basophilic Cell Leukemia

While basophilic cells are more common in chronic myelogenous leukemia than in other conditions, types of leukemia have been reported in which the basophile predominated

The symptomatology and course are like that of acute or chronic myelogenous leukemia The leukocyte count may reach 500 000 per cu mm with 83 per cent basophiles[1] There may be progressive anemia and thrombocytopenia A remission may be produced by x ray therapy Fever splenomegaly and hepatomegaly occur as in myelogenous leukemia In the liver there is myeloid infiltration around the portal canals The basophilic nature of the cells quite evident in fresh blood and bone marrow films may not be evident in fixed tissue taken at autopsy[180]

Agnogenic Myeloid Metaplasia

This syndrome, the name of which was introduced by Jackson Parker and Lemon[187] confused with chronic myelogenous leukemia because of the enlarged spleen and the leukemoid blood picture has been found in a few patients 10 cases were described by them Carpenter and Flory[181] summarize the features as follows (1) osteosclerosis and fibrosis of the marrow cavities (2) compensatory myeloid tissue in the spleen and liver with resultant splenomegaly (3) a blood picture characterized by a decrease in the erythrocytes leukocytes and platelets together with the presence of small numbers of immature red and white cells and occasional megakaryocytes

The condition may result from any process, which causes slow myeloid aplasia with compensatory myeloid metaplasia The etiology may be sclerosing tumors chemical poisoning as phosphorus strontium benzene and carbon tetrachloride osteosclerosis associated with blood dyscrasias and Albers Schonberg s disease marble bones[8 6] The compensatory metaplasia may result in overgrowth of the cells polycythemia

As the source of blood cells is transferred from the bone marrow to the spleen x ray therapy is contraindicated[1 86] The survival period may be as long as 20 years[1 7]

The symptoms include weakness abdominal distress and a tendency to hemor rhage The spleen is enlarged and hard, and the outlines are normal The spleen may be slightly or markedly fibrotic with foci of bone marrow growth Similar areas may be found in the liver and lymph nodes While the bone marrow may show fibrosis or aplasia some hyperplastic areas may be present at times Several cases encountered early in the disease and followed for years started out with a displacement of the marrow by lymphoid cells, lymphoblastomatous transformation followed by aplasia and fibrosis

Leukemoid Conditions

High leukocyte counts with an orderly increase in the number of immature forms may be found in many conditions and simulate leukemia

The *polymorphonuclear neutrophiles* may be increased in number in the following conditions carcinomatosis of the bone marrow[1 8] carcinoma of the bladder with metastasis to the lungs and prostate[180], subchronic arthritis[1 0] bothriocephalus anemia after pneumonia[170] fibrosis of the bone marrow[181 1] , acute infections septicemia bone marrow intoxication (mustard gas)[146], toxic reaction to mercurial ointment[1 4] tuberculosis[19] bee stings[190], Hodgkin s disease von Jaksch pseudoleukemia Mediterranean erythroblastic anemia subacute bacterial endocarditis hemolytic anemia polycythemia vera[1] , diabetic coma[198]

The *eosinophile cells* may be increased markedly in number in some patients with acute colitis[11] Hodgkin s disease and ulcers of the sigmoid colon [1] (see also under Eosinophilic Leukemia)

Myoblasts have been noted in increased numbers in tuberculous sepsis *Lymphocytes* have been increased markedly in measles, pertussis acute infection[14] varicella and pseudomucinous cyst of the ovary [4] The *leukocyte count in infectious mononucleosis* may be markedly elevated and may simulate lymphatic or atypical cell leukemia

Leukopenic conditions may simulate the aleukemic forms of leukemia Among these diseases are agranulocytosis miliary lesions of the bone marrow neoplasm tuberculosis and aplastic anemia

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CHAPTER XVIII

POLYCYTHEMIA

By BENJAMIN ALEXANDER

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Introduction

Definition and Classification

Literally polycythemia means increased cellular elements in the blood. Clinically it denotes a condition in which there is an abnormal increase in the number of circulating erythrocytes. The diseases in which this occurs may be classified into two main groups:

1. Polycythemia vera (erythremia), a disease or group of diseases in which the absolute and relative number of erythrocytes in the body is increased although there is no dehydration or disturbance of blood oxygenation.

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II Erythrocytosis This group may be subdivided into three separate categories

A A polycythemia in which only the relative number of erythrocytes per unit volume of blood is increased, and which develops in disorders that produce severe dehydration and hemoconcentration

B A polycythemia which is both relative and absolute and which occurs in conjunction with diseases that interfere with adequate oxygenation of the blood

C A type of polycythemia which is obscure and which appears as an incidental manifestation in various miscellaneous conditions

Background

Historical

In 1854 Vogel[1] found that the number of erythrocytes was increased in certain conditions and he clearly indicated the importance of distinguishing between "absolute" and "relative" changes in red cell number Eighteen years later Naunyn observed some cases of chronic heart disease in whom the amount of circulating hemoglobin was greater than normal and in 1890 Viault[3] noted the polycythemic nature of the blood of animals and humans who lived at high altitudes Subsequent work by numerous physiologists demonstrated the close relationship between the tension of oxygen in the arterial blood and the number of circulating erythrocytes This furnished the basis for designating those forms of *polycythemia arising from factors interfering with adequate oxygenation* of the blood as "secondary erythrocytosis", a physiological and clinical entity clearly distinguishable from that form of polycythemia reported by Vaquez[4] in 1892 His subject showed splenomegaly in addition to polycythemia and plethoric cyanosis and yet presented no abnormality that could conceivably, have resulted in arterial oxygen unsaturation Similar observations thereafter by such eminent clinicians as Rendu and Widal[5] Turk[6] and Osler[7] made the disease well known and established the fairly clear cut characteristics of this syndrome now referred to by various terms such as polycythemia vera (rubra) Vaquez Osler disease primary erythremia splenomegalic polycythemia myelopathic polycythemia, erythrocytosis megalosplenica Specific classification awaits elucidation of the etiology of this clinical entity

Physiological

Despite considerable advances in our knowledge concerning the factors which control hemopoiesis little is known regarding the mechanisms whereby the formed

elements of the blood are maintained relatively fixed at their normal levels To realize the extent of our ignorance we need only recall how incomplete is our concept of the sequence of events set in motion by acute hemorrhage with a) alteration in the overall diameter of the vascular tree b) redistribution of blood from hemopoietic reservoirs and c) mobilization of the blood forming capacity of the bone marrow reflected in the outpouring of less mature erythrocytes The regeneration of both red cells and hemoglobin proceeds only until the normal levels of both are again attained Without doubt the complex relationship between the oxygen-carrying power of the blood and the erythrogenic activity of the bone marrow is of fundamental importance in this connection Similarly the administration of certain hemopoietic factors to anemic subjects suffering from their lack stimulates blood production until but only until the normal state is again attained even if the substances are given in excess Thus both in hemorrhage and in anemia from other causes blood regeneration for some obscure reason ceases when normal values are again reached

Increase in the number of circulating erythrocytes occurs under certain physiological conditions such as vigorous exercise emotional excitement and discharge of epinephrine into the circulation[8,9,10] This polycythemia always transient and of mild degree results from splenic contraction and intravascular redistribution of the red cells the total red cell mass in the body remains unaltered

Polycythemia can be induced experimentally by interference with adequate oxygenation of the blood and tissues and also by the administration of certain chemical agents[11,12,13] Restoration of normal oxygenation or removal of these substances results in reduction of the red cell count to normal It is clearly evident that while the fundamental mechanism controlling the relative or absolute number of circulating erythrocytes may thus have been affected temporarily it was not altered permanently Little is known concerning the process underlying this phenomenon

Erythremia (Polycythemia Vera)

Etiology

Erythremia is a rather uncommon chronic disease insidious in onset and course Its outstanding characteristics are an increase in the relative and absolute number of circulating erythrocytes associated with increased erythroblastic activity of the bone marrow Although it usually affects individuals between the ages of 35 and 65 the condition has been observed even in children the youngest recorded case is that of Holbertsma[14] in a child of six A familial tendency to the disease has been reported[15,16,17] While the disorder occurs in all races Reznikoff and his associates[18] and others[19] found a higher incidence in Jews which because

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Pathological Anatomy and Physiology

Erythremia is a disorder in which increased erythroblastic leucoblastic and thromboblastic activity occurs These abnormalities are found in most cases in the bone marrow and occasionally in the extramedullary hemopoietic regions such as spleen, liver and rarely kidney

That there is intense hyperplasia of the erythrogenic elements has been well recognized The red marrow considerably increased in volume at the expense of the fatty marrow resembles grossly that found in Addisonian and hemolytic anemia Microscopically it appears filled with large numbers of red cells in various stages of maturation Not infrequently mitoses may be seen In contradistinction to what obtains in pernicious anemia however megaloblasts are not found

Less generally known is the fact that in many cases the marrow also shows increased leucoblastic[39, 40] and megakaryocytic activity[41, 42] which often is reflected in the peripheral blood The former possibly indicates a close relationship between erythremia and leukemia which is suggested also by many clinical observations referred to later Microscopically the marrow reveals increased numbers of promyelocytes myelocytes and young granulocytes as well as megakaryocytes In the presence of anemia as happens occasionally in some erythremics consequent to acute hemorrhage these findings in a marrow specimen may be very helpful in establishing the diagnosis

The abnormally high total blood volume the elevated hematocrit and the increased number of circulating erythrocytes appear to be related directly to the marrow hyperplasia *The hypervolemia is referable to the huge total red cell mass* the plasma volume being essentially normal[13] Although the erythrocytes usually range between 7 and 10 million per cubic mm counts as high as 17 or more million are encountered occasionally The maximum number of red cells which can be crowded into a unit volume of blood theoretically is limited by the mean corpuscular size It is unlikely that counts much higher than 15 million can occur since this would presuppose erythrocytes which average 60 cu micra in volume (normal about 90) even if we assume a hematocrit of 90 per cent cells and only 10 per cent plasma[6] While some degree of microcytosis does occur in erythremia it is not of this magnitude

A direct consequence of the abnormally large red cell concentration is an increase in blood viscosity which may be six or more fold greater than normal[12] This together with the greatly augmented blood volume is the basis for much of the clinical picture of the disease The great and lesser veins and also venules are distended and engorged and the capillaries are elongated and tortuous especially in their venous segments Because of the increased viscosity blood flow at least in the periphery is retarded greatly[44, 45, 46] Although one would expect these phenomena to result in disturbances in hemodynamics with an increased load on the

of the frequency of thromboangeitis obliterans in this group led these authors to study the vascular tree of erythremic marrow with results referred to later

None of the several theories, which have been proffered for the etiology of erythremia, has been substantiated The older concept that the increased number of red cells was attributable to an abnormally long life span of the erythrocyte with an inhibition of the normal mechanism for red cell destruction is incompatible with the finding in all cases of erythroblastic hyperactivity of the marrow Unsuccessful attempts have been made to link the pathogenesis of the disease with certain substances important in hemopoiesis That the disease is referable to excessive elaboration of antianemic factors, which are present in gastric juice or which arise from interaction of intrinsic and extrinsic factors in the gastrointestinal tract probably can be excluded by the fact that antianemic liver and stomach preparations administered to normal individuals do not increase the red cell count [0] Nevertheless, several investigators [1 ?? 3] have treated erythremics by gastric lavage on the basis that removal of "addisin" would decrease *the supply* of this hemopoietic material The reported results are variable and inconclusive

The close relationship between the number of erythrocytes in the circulating blood and the oxygen tension in the marrow suggests that erythyremia may be due to decreased oxygen supply to this organ Demonstration by Reznikoff and his associates[18] of changes in the vascular tree of erythremic marrow lends support to this theory Although the high incidence of generalized vascular disease involving *both the large and small vessels in erythremia is also impressive* in this connection direct demonstration of a reduced oxygen tension in the marrow is necessary to confirm this etiological concept

More recently it has been reported [4–5 ?( )–6] that some cases give a history of long exposure to toxic chemicals in the form of benzol and related organic solvents We too have been impressed by the frequency with which erythremics have occupations (rubber cement workers painters printers tailors metal part cleaners etc) that have one thing in common the use of organic solvents containing benzol and related compounds The incrimination of these agents, also in the etiology of aplastic anemia and certain leukemoid conditions on the one hand and the close inter relationship between polycythemia vera, anemia and leukemia on the other (see later on in this chapter) make these chemicals suspect as possible etiological agents in some cases More observations however are necessary to substantiate the validity of this hypothesis

Of interest is the frequency with which other well known clinical entities coexist in erythremic subjects A high incidence of peripheral vascular disease in the forms of thromboangeitis obliterans arterio and arteriolo sclerosis and erythromelalgia has been reported[18 7–8 9 30 31] In addition gout[3?] and also peptic ulcer[33 34 35 36 37 38] are said to occur with abnormal frequency The significance of the possible inter relationships between erythremia and these diseases is obscure

Symptoms

Most of the symptoms aside from those related to thrombotic episodes are based upon the increased blood viscosity and hypervolemia. These symptoms, as paradoxically in anemia, probably reflect tissue anoxia which may result from the sluggish circulation in the capillaries and from the decreased coefficient of oxygen utilization found in polycythemia vera.[1]

The disease is insidious in its onset and course. Not infrequently the patient is unaware of anything untoward until a sudden vascular occlusion occurs drawing attention to the underlying disorder. In other patients symptoms referable to the nervous system often are the first indication of the disease.[67] Headache, a vague feeling of fullness in the head, dizziness, somnolence, visual disturbances, paresthesia, syncope, fleeting paresis or paralysis, insomnia and tinnitus are the most common. Of the psychic disturbances forgetfulness, transient loss of memory, increased irritability, hallucinations and mental depression occur most often. Occasionally an erroneous diagnosis is made such as neurosis, psychosis or organic brain lesion. Osler[7] early drew attention to the similarity between these symptoms and those of mountain sickness. In both diseases they probably result from tissue (brain) anoxia despite the greatly increased oxygen carrying power of the blood.

Gastrointestinal symptoms also are common. These often mild include a feeling of fullness in the abdomen, dyspepsia with gas and bloating, anorexia and constipation. Some of these complaints may be related to complicating disease of the liver. The more severe symptoms, e.g., nausea, vomiting and abdominal pain often point toward a serious complication such as mesenteric thrombosis or peptic ulcer with or without hemorrhage. Pain consequent to splenic infarction or the less distressing dragging sensation in the left upper quadrant associated with the weight of the spleen may add to the gastrointestinal symptoms.

Occasionally the first manifestation of the disease is intermittent claudication of the legs or cardiac pain indistinguishable from classical angina pectoris, both precipitated by exercise. While arteriosclerotic disease so commonly present in erythremia is undoubtedly a factor in the pathogenesis of these symptoms, the elevated blood volume and the increased blood viscosity must play an additional important role since these symptoms often disappear promptly when the hematocrit reading is lowered. They may recur at a later date when the arteriosclerosis becomes more advanced.

The great majority of erythremics have an elevated basal metabolic rate[68, 69] which results in excessive sweating and occasionally in loss of weight. The reason for the increased metabolism is unknown. Perhaps it is comparable to the hypermetabolism found in leukemia.

Other symptoms which not infrequently are the first to call attention to the

heart, surprisingly few abnormalities in cardiovascular physiology have been reported. Cardiac output, cardiac work and the arteriovenous oxygen difference generally have been found to be normal[47]. The velocity of blood flow (arm to tongue) also is unaltered or only slightly prolonged[47, 48].

Most observers are in accord as to the high incidence of vascular disease in erythremia. As many as 27 to 29 per cent. of patients are said to show peripheral vascular disease[9, 49] of one sort or another. Arteriolar and capillary lesions have been observed in various parts of the body[50,51, 5] and erythromelalgia is not uncommon[7, 37]. Frequent vascular occlusions[53] and gangrene of the extremities[54, 30,55] occur. There is furthermore a considerable literature concerning the possible relationship between erythremia and thromboangeitis obliterans[19, 9, 30, 31]. Most hematologists can recall some patients who present clinical and pathological evidence of this vascular disorder antedating, or coexistent with, the hematological dyscrasia.

The exact relationship, if there is any, between erythremia and leukemia is obscure. It is well known that many cases of polycythemia vera at some stage of the disease show bone marrow and peripheral blood evidence of hyperplasia of the myeloid cell series[39, 56, 57,58,59, 37]. Certain observers believe this represents a leukemoid reaction which is said to occur in about 17 per cent. of cases[38]. In a large number of these the picture resembles closely, if not indistinguishably, myelogenous leukemia[60]. There seems to be a good correlation between the duration of the erythremia and the development of a leukemoid blood picture with splenomegaly[38]. Some hematologists believe that erythremia and leukemia often co-exist or that the former may terminate as the latter, thus constituting a separate disease entity named erythro-leukemia[19]. Conversely, polycythemia has been reported also as developing in cases of typical leukemia[61, 6]. Such cases are referred to as leuco-erythremia. Despite these observations, however, the connection between these diseases remains hazy and confused.

Splenomegaly occurs in about 70 per cent. of all erythremics[63]. One of the chief causes of splenic enlargement is engorgement with blood, although some increase in the splenic pulp usually is evident. When enlarged, the organ is firm, often fibrotic and frequently the site of infarction with perisplenitis[64]. Splenic tuberculosis has been found also in some cases[65].

Hepatomegaly is associated frequently with the splenomegaly of erythremia, although it may appear independently. An enlarged liver is found in at least half the cases[45, 37], and often it is the site of a terminal cirrhosis[9, 66].

One of the most frequent complications of erythremia is vascular occlusion, venous or arterial, which may arise anywhere in the body, involving commonly the cerebrovascular, myocardial, splenic, portal, mesenteric, renal and peripheral circulations. Probably this is attributable to the sluggish circulation plus the increased platelet counts found in about 30 per cent. of cases[37].

the extremities where despite good pulsations of the arteries gangrene of the fingers or toes slowly supervenes simulating thromboangeitis obliterans Raynaud s disease or ergotism Symptoms of peripheral thrombophlebitis also are frequent but singularly enough embolic phenomena are rare

Physical Signs

The signs of erythremia usually are well defined The classical color of the skin and mucous membrane has been described already Fundiscopic examination of the eyes almost always reveals evidence of marked vascular engorgement and arteriosclerosis Occasionally some papilledema is seen which may lead to an erroneous diagnosis of serious intracranial pathology such as tumor

The lungs usually are quite normal although respiratory minute volume frequently is elevated especially following exertion The inconspicuous pulmonary findings are in direct contrast to what will be observed in erythrocytosis secondary to various pulmonary disorders This is true also with regard to the heart although it must be remembered that abnormalities may be detected in either organ as a consequence of infarction or other complications Some degree of cardiac enlargement may be detected occasionally especially in cases with hypertension Gaisbock[77] claimed that these particular patients constituted a different entity from erythremics without hypertension The former group which is said also to show absence of splenomegaly was referred to as polycythemia hypertonica Most students of the disease feel in accord with Orlowski[73] that the incidence of hypertension in erythremia is no different from that in nonpolycythemic individuals of the same age group with arteriosclerosis That there is any significant correlation furthermore between hypertensive erythremics and those with spleens of normal size i still uncertain

The high incidence of spleno- and hepato-megaly has been referred to already In some cases these manifestations antedate the appearance of the other classical features of the disease In others the reverse is true In those subjects who do not have enlargement of these viscera the differential diagnosis may be difficult between erythremia and secondary erythrocytosis where hepato- and splenomegaly are rare In passing it should be remembered that considerable splenic enlargement may be present before the organ becomes palpable

Examination of the extremities often will reveal evidence of peripheral arteriosclerosis or of the physiological disturbances characteristic of inadequate blood flow It is noteworthy however that occasionally trophic changes occur in the absence of extensive arteriosclerotic changes or major vessel occlusion Extensive gangrene of the toes may appear even though adequate pulsations of the dorsalis pedis and posterior tibial arteries attest to good blood flow through these vessels

pathological state, are those arising from an acute hemorrhage This is apt to be severe and at times fatal Uncontrollable bleeding following a simple surgical procedure like tooth extraction is common and may result in reduction of the red count from levels of 10 million or more to precariously low levels of 1 5 million requiring large transfusions Massive hemorrhage may occur also from a peptic ulcer which as indicated before, is found relatively commonly in erythremia The basis for the bleeding tendency is obscure All the known factors involved in blood coagulation apparently are normal with the possible exception of clot retraction which has been reported to be slow[1] This is not surprising in view of the evidence that a large red cell mass interferes with clot syneresis[70] This however cannot be the sole explanation, since even well treated polycythemics with normal hematocrit readings occasionally will bleed profusely following surgery Another factor, which must be considered, is the abnormal state of the capillaries and venules which, because of elongation and overdistention with blood may fail to contract properly following trauma an important and too often underestimated step in the normal mechanism of hemostasis In any event this hemorrhagic diathesis is bizarre in view of the thrombocythemia and the thrombophilic tendency in erythremia

Perhaps also related to the abnormal state of the peripheral circulation are the skin manifestations of this disease The striking color of the skin has been the subject of considerable interest Usually it is referred to as a plethoric cyanosis Especially prominent on exposed surfaces, the cheek, nose, ears, hands it is noticed frequently by the patient or his friends In those subjects with erythromelagic symptoms or with impending gangrene of the extremities the cyanosis in those regions is marked especially when they are in the dependent position The characteristic skin color vividly described by Osler[7] as 'red as a rose in hot weather and ' blue as indigo ' in winter is however not always present[71] This is particularly true following therapy, especially by periodic venesection The color of the mucous membranes of the tongue buccal mucosa and parietal conjuctiva also is characteristic The purplish red engorged appearance simulates that found in acute inflammation

Other symptoms referable to the skin include itching and sensitivity to cold These not necessarily coexistent or otherwise related often are extremely distressing and difficult to treat, persisting even after adequate therapy of the hematological picture

Thrombotic episodes produce symptoms whose characteristics depend upon the location of the vascular occlusion, the size and nature artery or vein of the vessel involved and the rate at which occlusion takes place Thus a patient may present the typical picture of acute myocardial infarction cerebrovascular accident, mesenteric or peripheral thrombosis, splenic, renal or pulmonary infarction etc More insidiously developing evidence of tissue anoxia occasionally appears in

firmatory evidence of panhyperplasia will point toward a diagnosis of erythremia even in the presence of anemia

Other blood abnormalities clinically less significant have been described The viscosity of the plasma is said to be less than normal[12] Blood uric acid is reported high[69] Blood clotting has been found hastened normal or delayed and clot retraction is said to be poor[9] The icteric index is normal or only slightly elevated Blood non protein nitrogen values as high as 40 to 50 mgm per 100 c c of blood are the rule and probably reflect embarrassment of renal function consequent to increased blood viscosity

The urine of high specific gravity unless there is extensive renal damage often contains a slightest possible or very slight trace of albumin occasional to several red cells white cells or both and a few hyaline and granular casts It is likely that in some cases these abnormalities also are to be explained on the basis of increased blood viscosity since they disappear upon restoration of the hematocrit reading to normal In other cases the picture may be more pronounced and persistent indicating degenerative disease of the kidneys

The basal metabolic rate frequently is elevated slightly to moderately[65 66] The roentgenologist occasionally helps in making the diagnosis by detecting increased vascular markings in the lungs due to vascular engorgement or spleno- and hepato-megaly in routine gastrointestinal examinations

Clinical Course

The clinical course usually is benignant and protracted occasionally extending to 10 or 15 years and rarely even longer Frequently death results from any one of the many complications commonly encountered in this disorder

There are two complications particularly to be feared The first is vascular occlusion which occurs chiefly in the brain heart mesenteric and portal systems and periphery Both the extensive arteriosclerosis and the thrombotic tendency consequent probably to the increased blood viscosity and thrombocythemia provide the basis for this untoward development

The second chief complication is hemorrhage Common sources of bleeding are from a tooth socket following dental extraction from the nose or from a peptic ulcer Hemorrhage from the latter may be fatal because of the sclerotic condition of the eroded vessel Bleeding from more accessible sites can be controlled effectively by recently developed methods of local hemostasis employing packs of fibrin foam with liquid thrombin

Other complications leading to progressive deterioration are cirrhosis of the liver and vascular disease of the kidneys Rarely as already pointed out the disease may progress gradually into a true leukemia with relatively rapid down hill course or into an aplastic type of anemia where the hyperplastic marrow finally becomes fibrotic[77 78 37]

Laboratory Findings

The laboratory findings in erythremia are striking As with all laboratory tests it is important to know where normality ends and abnormality begins Most hematologists agree that for males persistent red counts in excess of 6 2 million and hematocrit readings greater than 58 per cent cells are to be considered evidence of polycythemia For females the corresponding figures are 5 6 and 52 respectively In erythremia the red count usually is between 7 and 10 million and occasionally, more The increase in the hematocrit reading and in the circulating hemoglobin is not always proportionate to the increase in erythrocytes Underlying this discrepancy is a somewhat decreased mean corpuscular size and hemoglobin content[74 75 76] As will be seen later, therapeutic measures employing repeated venesection serve to decrease further the mean red cell dimensions and hemoglobin so that the volume and color indices become even lower Spontaneous variation in the red count, hematocrit reading and percentage hemoglobin occur from time to time Obviously when the disease is complicated by acute hemorrhage, these laboratory findings may be reduced significantly below normal

In most cases some degree of leucocytosis occurs during the course of the disease More often than not the white count will be normal or only slightly above normal when the patient is first seen but as the patient is followed over the years the count rises and may reach levels as high as 90 000 Usually however, the white cells do not exceed 40,000 per cubic mm

In addition to the leucocytosis the blood smear shows other evidence of marrow hyperactivity The percentage of polymorphonuclear leucocytes and of eosinophils is increased The hemogram also reveals a shift to the left (immaturity) in degree of maturation with band form polymorphonuclears and a few myelocytes and metamyelocytes More rarely even younger forms may be found Occasional to frequent nucleated red blood cells together with polychromatophilia, are seen in the smears of most patients In addition abnormally abundant platelets occur which occasionally reach levels of several million per cubic mm Those subjects with elevated erythrocyte leucocyte and thrombocyte counts can literally be said to have polycyt hemia

The degrees of polycythemia leucocytosis and thrombocythemia bear no strict relationship to one another Extremely high platelet or white cell counts may be encountered in cases where the number of erythrocytes is only moderately elevated and vice versa Occasionally particularly after a complicating hemorrhage sufficient to reduce the red cell count and hemoglobin concentration to abnormally low levels the exceedingly high white cell count and/or platelet count may draw attention to the possibility of an underlying erythremia In such cases examination of the marrow obtained by sternal or rib puncture by revealing con

or of the hemoglobin by reliable technique (Talquist not included) is also a valuable safeguard against making an erroneous diagnosis of psychoneurosis brain tumor neurasthenia angina pectoris, intra abdominal disorder peripheral vascular disease etc in those instances where erythremia is not clearly evident as the basis for the clinical picture It must be remembered however that normal or sub-normal values for these blood constituents may result in erroneous exclusion of erythremia particularly in those cases which have or recently have had a hemorrhagic complication

Although the differential diagnosis between polycythemia vera and erythrocytosis usually is simple in some subjects it may prove difficult In erythrocytosis an underlying pathological process such as chronic pulmonary or cardiac disease arteriovenous anastomoses etc capable of producing interference with oxygenation of the arterial blood should be discernible In such cases a determination of the per cent saturation of the arterial blood is of considerable diagnostic value since it will be significantly lower than normal in erythrocytosis in contradistinction to the normal values which are obtained in erythremia Although this laboratory test is of fundamental value in differentiating between the two diseases it should be emphasized that polycythemia vera may occur here in patients who also have sufficient pulmonary or cardiac disease to produce a significant degree of arterial oxygen unsaturation Other points in the differential diagnosis are taken up in the section under erythrocytosis (see Table I)

At times it is exceedingly difficult to distinguish mild erythremics from those rare subjects who although normal in all other respects have erythrocyte counts and hemoglobin concentrations slightly above what is generally considered normal Occasionally one will encounter a vigorous healthy male whose ruddy plethoric appearance together with an incidental finding of a slightly elevated red count suggests a true erythremia Many of these individuals have occupations in which they are exposed to outdoor weather Such patients can be distinguished from erythremics since the slightly abnormal laboratory findings show no progression and since the classical symptoms and signs of erythremia do not appear In these individuals furthermore hepato and spleno-megaly are absent and examination of the marrow reveals no abnormality As is true with borderline cases of many diseases repeated observation of the individual patient over a period of time usually reveals the correct diagnosis

Treatment

Since the etiology of polycythemia vera remains obscure treatment must be directed at amelioration of the pathological physiology Accordingly therapy consists of restoring the abnormally high hematocrit reading and blood volume to normal This may be accomplished in any one of three ways (a) by repeated

Differential Diagnosis

The diagnosis of erythremia can be made readily in the classical case by the typical symptoms and signs of insidiously developing increased blood viscosity together with the laboratory findings of elevated red cell count high hemoglobin concentration, increased hematocrit reading leucocytosis and thrombocythemia It is important to exclude erythrocytosis as well as acute polycythemia such as occurs in diseases resulting in severe dehydration The finding of spleno- and hepato-megaly is helpful not only in this regard, but also in that it draws attention to the possibility of a blood dyscrasia in those erythremics whose first clinical manifestations may be those of a neurologic or psychiatric nature or of a vascular occlusion The routine determination of the number of circulating erythrocytes

TABLE I

DIFFERENTIATING POINTS BETWEEN ERYTHREMIA AND ERYTHROCYTOSIS

	Erythremia	*Erythrocytosis*
Intrathoracic Disease	Rare	Common
Cyanosis	Mild	Moderate to severe
Dyspnea	None or mild	Moderate to severe
Splenomegaly	In over 70% of cases	Rare
Hepatomegaly	In over 50% of cases	Rare
Hemorrhage	Common	Rare
Vascular Occlusions	Common	Rare
Red Blood Cells		
Number	Increased moderately to greatly	Increased mildly to moderately
Size	Tendency to microcytosis	Slight tendency to macrocytosis
Nucleated	Present	Absent
Reticulocytes — c	Normal	Increased
White Blood Cells		
Number	Increased at time markedly	Normal or slightly elevated
Differential	Shift to left	Normal
Platelets	Often increased	Normal
Arterial Oxygen Saturation	Normal (93–100%)	Reduced almost always to less than 85%
Blood Bilirubin	Normal or very slightly elevated unless hepatic complication present	Slightly to moderately elevated
Plasma Volume	Normal	Decreased

*Except erythrocytosis occurring at high altitudes or as a result of poisoning with certain chemicals

100 per cent 14 0 0 15 5 gms per 100 c c of blood and in most cases this can be accomplished by venesection of approximately 500 c c monthly or bimonthly

The interval between bleedings can be increased by implementing the treatment with an iron poor diet by means of which the negative balance of this element consequent to the artificially induced chronic blood loss can be enhanced The chief objection to this regime is that the diet which necessarily excludes such iron-containing foods as meats liver eggs whole grains and fruits and vegetables rich in iron is extremely monotonous and burdensome There is furthermore considerable danger of nutritional inadequacy since such foods are important sources of the B complex vitamins Accordingly it would seem desirable to permit the intake of a normal diet

The institution of chronic iron deficiency by means of controlled blood withdrawal has proved highly effective in the management of erythremia Objections to this form of therapy center around the concept that it may result in further stimulation of the already hyperplastic marrow Evidence supporting this is furnished by those occasional patients under active treatment whose high red cell counts drop appreciably when the negative iron balance is rectified by the administration of iron containing medications It has been shown by numerous observers[50 51 52] however that venesections of up to 500 c c of blood in erythremics do not result in increased hemopoietic activity as indicated by the absence of significant increase in reticulocytes Furthermore experience has indicated that patients are controlled readily and do fairly well for many years on this form of therapy

Reduction of the Red Cell Mass by Hemolytic Agents — The hemolytic agents employed most commonly in the treatment of erythremia are phenylhydrazine or its derivatives This substance first introduced by Eppinger and Kloss[53] damages the red cells and thus renders them more susceptible to the normal process of hemolysis As a rule the drug is administered orally in the form of capsules containing phenylhydrazine hydrochloride in doses of 0 1 gm (gr 1½) 2 or 3 times daily until a total dose of 3 to 4 grams has been given or until clinical evidence of hemolysis appears The chemical is cumulative in its action following its discontinuation hemolysis continues for 7 to 10 days Accordingly this interval during which red counts should be done every other day should be allowed to elapse before the full therapeutic effect is evaluated Usually this dosage will reduce the count to normal If not the course of therapy may be repeated with small doses totalling not more than 1 gm For maintenance 0 2 to 0 4 gm once a week usually is sufficient the exact amount to be determined by the symptoms and by the laboratory examination which should be done at least monthly Sudden large increases in dosage should be avoided since certain cases have been found to be highly sensitive to small increments in the dose and the boundary between apparent inaction of the drug and acute hemolysis is small[54]

withdrawal of blood (b) by destroying red cells with hemolytic agents, (c) by curtailing the erythroblastic activity of the hemopoietic organs with x rays or radioactivity Each method has its proponents and critics, and each its advantages and disadvantages [9]

Controlled Venesection — In the early treatment of erythremia repeated bleeding is the method of choice Removal of 500 to 700 c c of blood daily or every other day until the red count and hematocrit reading return to normal almost always results in dramatic improvement in the signs and symptoms of the disease While larger amounts of blood may be withdrawn safely from most erythremics within the first few days, certain patients react unfavorably by experiencing sudden syncope or weakness and collapse This therapeutic procedure clearly resulting in an artificially induced acute hemorrhage, serves to relieve the untoward effects of the greatly increased blood volume and viscosity As many as 8 to 10 venesections of 500 c c may be necessary When these are spread over a period of many days opportunity i afforded the tissues and vascular system to adjust gradually to the altered blood volume

Thereafter, phlebotomy should be performed as often as is indicated by the symptoms and signs and by the hematocrit reading Because of the striking relief provided by this procedure most patients soon learn the indications for blood letting and often can predict with remarkable accuracy increases in their hematocrit One cannot state arbitrarily at what levels it should be maintained since some patients feel weak and exhausted at values at which others have no symptoms Conceivably this may be related to variations from one individual to another in the coefficient of oxygen utilization of the tissues In general we have *found that most erythremics do well at a hematocrit of about 50 per cent* slightly less for females

The red count is a poor indication of the need for blood withdrawal For as time goes on and the patient undergoes periodic phlebotomy the number of erythrocytes reduced to normal following the first venesections, will ri e gradually, while the hemoglobin and hematocrit reading remain relatively stationary This is because the patient has now entered the therapeutic phase of artificially induced chronic blood loss which results in depletion of the body stores of iron Red cell regeneration continues but hemoglobin formation is curtailed because of lack of this essential element Accordingly a decrease in the mean corpuscular size and hemoglobin content ensues and the picture becomes that of relative hypochromia and microcytosis at a high level of red count The hematocrit reading at which therapy is directed now is reflected more accurately by the blood hemoglobin than by the number of erythrocytes Since the facilities necessary for routine determination of the hematocrit reading are not generally available in office practice the physician can just as satisfactorily be guided by an accurate determination of the hemoglobin It should be maintained at between 90 and

While satisfactory remissions for variable intervals of time are obtained in most cases, it is too early to state the required dosage or to evaluate fully the effectiveness of this therapeutic agent. Its use furthermore is not always unattended by complications. Leukopenia, thrombocytopenia, anemia and acute leukemia have been reported[104,105]. Apparently radiophosphorus, aside from its convenience and the fact that it does not produce radiation sickness, offers no advantage over the more conventional sources of radiation. Other agents such as arsenic in the form of Fowler's solution have been used also with some success[106,107].

Of the three general methods of treatment described above we are in complete accord with other hematologists[49,108,109,82,110], who feel that controlled venesection is in general the safest, most physiological and most effective means of controlling erythremia. Occasionally the other agents employed independently or in conjunction with phlebotomy[79] are found useful.

It is exceedingly important with any therapeutic method to check the blood often in order to guard against excessive destruction of blood or hemopoietic tissue. In this connection it should be pointed out also that erythremics may find their erythroblastic marrow of great advantage during a hemorrhagic episode. Those whose marrows have been curtailed by radioactivity or x radiation may be unable to respond as well to the strain imposed by this all too frequent complication.

Whereas most of the manifestations of the disease can be treated effectively by any one of the above methods of reducing the circulating red cell mass, certain symptoms and complications occur and persist despite treatment. Itching of the skin and poor tolerance to heat and cold occasionally are distressing and resistant to all therapeutic measures. Also hemorrhage, thrombotic episodes, hepatic cirrhosis, aplastic anemia and leukemia occur even in those cases whose hematocrit readings have been maintained within relatively normal limits.

Prognosis

The course of uncomplicated erythremia may last over 15 years, although the average duration of life after the disease is first diagnosed is 6 to 8 years[111]. Rarely complete remission may occur[11]. Because of the frequency with which fatal complications arise, however, the prognosis always should be guarded.

Erythrocytosis (Secondary Polycythemia)

Hemoconcentration

An acutely developing polycythemia occurs in those diseases which produce sufficient dehydration to cause hemoconcentration. Under such conditions the increase in red cells is only relative, the total red cell mass remaining normal.

Treatment with phenylhydrazine not infrequently results in thromboses[85] or in *an extremely rapid and severe hemolytic crisis which may prove fatal* For these reasons the drug should not be used on patients who are bedridden who are over 60 years of age, who have advanced arteriosclerosis or who have had previous thrombotic episodes[84] Obviously this limits considerably the number of subjects in whom phenylhydrazine may be used without danger

These limitations in addition to variation in the potency of the drug depending upon the freshness of the preparation have resulted in its general abandonment as an important therapeutic agent More recently acetyl phenylhydrazine introduced by Bodansky[86], has been used by many hematologists[87 88 79] in preference to phenylhydrazine because the former is practically as effective is less toxic and has a greater margin of safety than the latter The dose is 0 1 gm a day orally for 7 to 10 days followed by a rest period of about 2 weeks If required a second course may be given The usual maintenance dose is 0 1 gm every 5 to 7 days

The hemolytic effects of either of these drugs become manifest by the appearance of increased plasma bilirubin by dark colored urine and by decreasing red count The possible deleterious effect of freeing large amounts of the products of hemoglobin and red cell disintegration into the circulation cannot be overlooked especially in those cases complicated by cirrhosis of the liver, splenomegaly or renal disease To these objections must also be added the one raised against venesection, namely, that reduction of the circulating hemoglobin may serve to stimulate even further an overstimulated marrow

Use of X radiation and Radioactive Materials — The effects of x radiation on the hemopoietic system are well known Since this physical agent was first used in the treatment of erythremia by Bucky[89], numerous observers have established its therapeutic value[90–98] In general the procedure consists of the administration of 20 to 50 r daily or every other day for a total of 200 to 1 000 r depending upon the reaction of the patient Individual doses are applied alternately to anterior and posterior parts of the torso from knees to neck Usually about 500 r are required to produce substantial decrease in the erythrogenic activity of the marrow In most cases the hematocrit becomes normal within 2 to 3 months occasionally a second course of treatment applied cautiously, may be necessary A white count of less than 5 000 per cubic mm is an indication for discontinuance of radiation It must be remembered that individual patients differ in sensitivity and in required dosage For more details of the technique the reader is referred to the literature

Recently with advent of newer developments in atomic physics radioactive isotopes of atomic elements particularly P_{32} have been used effectively in the control of erythremia[99 100 101 102 103] The radioactive phosphorus may be administered orally or preferably intravenously, in the form of sodium acid phosphate

is less in the latter than the former Splenomegaly is rare if not absent in erythrocytosis unless there are additional complicating factors (see later in this chapter)

The highest red counts among residents of high altitudes are to be found in those whose physiology is further complicated by pulmonary fibrosis consequent to silicosis as occurs in Andean mine workers or who present a clinical picture known as mountain sickness or soroche[119] This disease quite prevalent among those residing under such barometric conditions is directly or indirectly attributable to the decreased oxygen tension of the inspired air since return to sea level is fairly promptly curative The acute form of this disease probably representing an as yet incomplete adaptation to decreased oxygen tension is to be distinguished from the subacute or chronic form where adaptation already satisfactorily developed fails for some inexplicable reason The breakdown is best interpreted as failure in the mechanism which enables man after a certain period of acclimatization to live in regions where habitation is difficult The cause and underlying nature of this failure is obscure In some cases silicosis or other pulmonary disorders may be found as the basis for the insufficiency Most cases however show no such abnormality The oxygen carrying power of the blood i e hemoglobin concentration is if anything higher than that of other individuals who residing at the same altitude are in full compensation

The clinical manifestations of mountain sickness bear a striking resemblance to those of erythremia[7 119] The symptoms are numerous the most common being weakness drowsiness dizziness faintness temporary blindness or deafness paresthesiae personality emotional and memory changes purpura and other hemorrhagic phenomena Anginal pain abdominal distress nausea vomiting and diarrhea are not uncommon The patient has a plethoric cyanosis with congestion and dilatation of the skin capillaries and venules The thorax is emphysematous which is characteristic of most individuals who reside at high altitudes The spleen is said to be enlarged in 12 per cent of the cases

Marked erythrocytosis of between 7 and 1 million red cells per cubic mm is always found together with an increased blood volume referable to the increased mass of circulating red cells Although the per cent oxygen saturation of the arterial blood 76 to 83 per cent is no lower than that which is found in well adapted individuals the arteriovenous oxygen difference is less due to the high oxygen content of the venous blood[119] This is said to indicate a decreased ability of the tissues to utilize oxygen

Following descent to sea level the disease is cured with restoration of all blood abnormalities to normal

Chronic Pulmonary and Cardiac Disease — The physiological and clinical studies demonstrating the close relationship between erythrocytosis and decreased oxygen supply in the inspired air provide an explanation for the polycythemia so

This type of erythrocytosis is encountered frequently in such disorders as cholera from shock states, from hemorrhage trauma or burns from diabetic coma, from excessive diarrhea, vomiting or sweating or from any other disorder which leads to serious depletion of body fluids It is important that this form of polycythemia which usually is transient, should not be confused with more serious forms of this abnormality

Anoxia

High Altitudes — Acute erythrocytosis is encountered also in sudden ascent to high altitudes, presumably as a result of splenic contraction with mobilization and redistribution of red cells formerly stored in the spleen and in other hemopoietic depots This also, is the mechanism whereby sudden partial asphyxia or acute CO poisoning produces increases in the number of red cells in circulation Strictly speaking, this cannot be termed an absolute polycythemia, since there is no increase in the total number of erythrocytes in the body

An absolute erythrocytosis is, however found in people who reside at high altitudes or who are subjected for a prolonged interval of time to atmospheres of decreased barometric pressure[113, 3, 114] Ample studies[115] have demonstrated conclusively that in general there is a striking proportionality within certain limits, between the degree of anoxemia and the degree of polycythemia There are considerable variations from individual to individual This erythrocytosis in contradistinction to that produced abruptly by balloon or aeroplane ascensions appears after several days of living under conditions of reduced oxygen tension It is found also in those who have been exposed intermittently to high altitudes e g aviators and employees on trains traversing mountain ranges[115] The erythrocytosis so induced may attain levels of as high as 8 million red blood cells per cubic mm and is accompanied by reticulocytosis and evidence of increased erythpoietic activity of the marrow[116, 114, 11] Under such conditions the blood volume is elevated[115, 117] due entirely to an increase in the total mass of circulating erythrocytes Maximal polycythemia occurs at altitudes resulting in about 70 per cent arterial oxygen saturation At higher altitudes lower values of red cell number are observed[118, 115] The erythrocytosis disappears after elimination of the anoxia

Certain other hematological effects of long exposure to atmospheres of reduced oxygen tension are noteworthy because they are of value in distinguishing between this erythrocytosis and erythremia In the former there is a slight tendency to macrocytosis[115], whereas in polycythemia vera the red cells are either normal or slightly reduced in size[74, 7, 76] Nucleated red cells, not infrequently found in erythremic blood[56, 74] are absent in erythrocytosis[115] Leucocytosis is seen only temporarily and to a relatively slight degree in residents of high altitudes in contradistinction to what obtains in polycythemia vera[115] The blood bilirubin also

the most severe degrees of polycythemia are found in congenital heart disease with pulmonary stenosis[126, 127, 125, 128, 129] The red count may be as high as 13 million but usually is between 7 and 8 5 million Some cases show increased hemopoietic activity with disappearance of the yellow fatty marrow Rarely spleno and hepato-megaly develop whether they are referable to the polycythemic condition congestive heart failure or cardiac cirrhosis of the liver is not clear In this disease as in erythrocytosis secondary to pulmonary disease or residence at high altitude the total red cell mass and blood volume are increased The plasma volume frequently is diminished

Polycythemia of milder degree is found occasionally in other forms of heart disease particularly in mitral stenosis of long standing It may be that this is related to the fibrotic changes which develop in the lungs consequent to the heart lesion

In most instances the differential diagnosis between erythremia and the erythrocytosis of pulmonary and cardiac disorders is relatively easy chiefly because the basis for the anoxemia of the latter often is clearly evident Occasionally however it is difficult to make the distinction especially where chronic pulmonary or cardiac disease may unrelatedly coexist with erythremia The chief differential points are summarized in Table I An accurate diagnosis is extremely important since reduction of the red cell mass is the therapeutic goal in erythremia whereas in secondary erythrocytosis such treatment may be fatal[128]

The question of venesection or other procedures to reduce the hematocrit reading frequently arises in connection with the treatment of erythrocytosis Since the elevated red count and hemoglobin in this disorder represent an effort on the part of the individual to compensate for a decreased supply of oxygen to the tissues it would seem illogical to interfere with this compensatory mechanism On the other hand the extreme degrees of erythrocytosis encountered in pulmonary fibrosis Ayerza s disease or congenital heart disease result in abnormally increa ed blood viscosity and hypervolemia with their untoward signs and symptoms In such instances it appears justifiable to reduce the red cell number by cautious small venesections 250 c c guided always by the patient s condition Obviously the aim is not to reduce the hematocrit reading to normal but rather to permit a degree of polycythemia which will provide an increment of oxygen to the tissues and yet which is not severe enough to provoke the undesirable effects of increased blood viscosity and volume Admittedly this is as difficult as steering between Scylla and Charybdis

Other Conditions — Intermittent or continuous exposure to non fatal concentrations of carbon monoxide also can cause erythrocytosis in animals and man[130, 131, 132, 133] which occasionally reaches levels as high as 9 million red cells The gas acts by combining with hemoglobin thus reducing the oxygen carrying power of the blood and interfering with adequate oxygenation of the tissues

often found in subjects suffering from various chronic pulmonary and cardiac disorders The increase in the number of circulating erythrocytes in these conditions is best interpreted as an effort to compensate for inadequate oxygenation of the arterial blood

Among the more common pulmonary diseases in which polycythemia is found are those which produce abnormalities in the lungs interfering with proper gaseous exchange *Advanced pulmonary fibrosis from any cause* bronchial or tracheal stenosis intrathoracic tumors spontaneous or induced pneumothorax of relatively long duration chronic cystic disease of the lungs etc may result in erythrocytosis In these cases a significant degree of arterial oxygen unsaturation is almost always present That this, however, cannot be the sole factor is evidenced by the fact that polycythemia is observed rarely in uncomplicated chronic pulmonary emphysema with oxygen unsaturation[10]

It is furthermore important to remember that, as with the polycythemic response to high altitude great individual differences exist in the marrow response to different degrees of arterial oxygen unsaturation[11] Whereas one individual may exhibit polycythemia at let us say, 80 per cent arterial oxygen saturation another will have a normal red count at the same level In addition, the degree of arterial oxygen saturation at basal conditions is no indication of what it will be during exercise For example, intermittent arterial oxygen unsaturation following exercise or other physical activity in individuals with impaired pulmonary ventilating capacity i e decreased pulmonary reserve may lead to erythrocytosis, even though the degree of oxygen unsaturation at rest may not be significant This is analagous to the erythrocytosis already discussed which develops in subjects who are exposed only intermittently to atmospheres low in oxygen tension

In any of these conditions the erythrocytosis rarely attains levels commonly observed in polycythemia vera There is however one syndrome in which the degree of erythrocytosis is comparable to that found in erythremia namely Ayerza's disease Red cell counts as high as 10 to 11 million per cu mm are not uncommon This disorder, first described in 1901 by Ayerza[11a] and labelled "cardiacos negros " becomes clinically manifest by chronic cyanosis of variable but usually severe degree and is associated with evidence of pulmonary emphysema and marked dilatation and hypertrophy of the right heart, whose ventricular wall is often as thick as the left There is a long history of asthma and bronchitis with marked and progressive dyspnea on exertion Clubbing of the fingers and toes is common The spleen may be enlarged[12] although by no means as frequently as in polycythemia vera These manifestations long antecede the development of congestive heart failure Sclerosis and dilatation of the pulmonary artery commonly are found at autopsy Some observers attribute the disease to syphilis[13,14], but others[15] do not believe that syphilis is an etiological factor

With regard to cardiac disorders complicated by secondary erythrocytosis

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Some acclimatization takes place as the per cent hemoglobin in the blood increases

It is also stated frequently that erythrocytosis occurs following exposure to nitrites and aniline products, such as acetanilide, which convert hemoglobin to methemoglobin[1]

Miscellaneous

Polycythemia may be produced by a large number of chemical agents[4] The more important ones among these include sulphur thorium x radium chloride phosphorus arsenic, opium and nicotine The mechanisms of their action are obscure

Other diseases in which polycythemia may occur rarely are encephalitis lethargica and Huntington's chorea[134] and to a moderate degree in pituitary basophilism[135] or in the virilizing tumors of the adrenal gland[136] The type of polycythemia found in these disorders has not been elucidated

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CHAPTER XIX

PURPURA AND PURPURIC STATES

By HENRY A CHRISTIAN

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combination of these and serum or exudate with or without hemorrhage may escape through the epithelium of the skin and collect just beneath the cornified layer to make vesicles or blebs of varying content. Thus very complicated skin lesions may develop. This is seen particularly in the group of anaphylactoid purpuras. Furthermore in recurring attacks as occur frequently the same form of skin lesion may not be repeated in each attack. Recurrent hemorrhage may dominate the clinical picture with a minimum of other local changes. With purpura of serous surfaces or mucous membranes often there are associated visceral symptoms such as arthralgia, abdominal pain, etc. Skin lesions other than purpuric, particularly telangiectatic lesions, may antedate or accompany the purpura and bleeding. Frequently with any of these there are familial or hereditary characteristics. With all of these possibilities the subject becomes very complicated and this makes difficult a satisfactory classification of purpura and related recurrent hemorrhages.

Before considering classification and other features of these several purpuric diseases an outline of normal hemostasis and the procedures to utilize in studying these patients will prove helpful.

Hemostasis in Normal Individuals

Since this chapter describes a variety of clinical complexes in which purpura or bleeding is an essential factor, it is important to understand the mechanism in normal individuals by which bleeding is stopped or prevented, i.e., hemostasis. The mechanism of hemostasis in normals, well reviewed recently by Frommeyer and Epstein[6], can be considered as dependent upon three factors acting in combination; these are (1) the extravascular factors such as location of blood vessels, the tone of surrounding tissues and the presence of tissue fluids; ( ) vascular factors such as size and structure of small blood vessels in different parts of the body and their tone, especially their contractility; and (3) clot formation factors such as the number and functioning of platelets[24] and the presence in proper amounts and properly functioning of the constituents other than platelets that bring about blood coagulation or thrombus formation.

In the normal subject hemostasis following injury causing hemorrhage occurs spontaneously and quickly because of the following series of mechanisms. When bleeding occurs from a small vessel, arteriole, capillary or venule, at once intravascular hydrostatic pressure falls and

INTRODUCTION

Terminology and Definition

Purpura is a term for multiple extravasations of blood into the skin, serous surfaces or mucous membranes The word etymologically is derived from Greek and Latin words meaning purple fish or purple color An earlier use of the term, purpura, was limited to blood extravasations into the skin, but as the word by derivation refers to the color of the lesions, it equally is applicable to extravasations elsewhere than into the skin and for a long time has been used in this broader sense The escape of blood into skin, serous surfaces and mucous membranes may be small, known as petechiae, intermediate in size, called macules or large, usually spoken of as ecchymoses or extravasations Gravity influences distribution in the cutaneous surfaces, petechiae and extravasations usually being more numerous and more prominent in dependent parts of the body When in purpuric states blood escapes into the skin, with rare exceptions it is confined there, while when the serous surfaces or mucous membranes are involved blood soon escapes to the surface, and there is bleeding into the cavity or viscus lined by serosa or mucous membrane resulting in hemarthrosis epistaxis hemoptysis hematemesis melena hematuria menorrhagia etc This difference between purpura involving skin and serous surfaces or mucous membrane depends on the character of the covering cells the skin with its stratified squamous epithelium with an external cornified layer being very resistant to the penetration to its surface of subepithelial collections of red blood cells while serous surfaces and mucous membranes which are covered by a thin layer of endothelial cells or a layer of single or sometimes moderately multiple columnar or cuboidal epithelial cells with or without cilia offer little resistance to penetration of red blood cells from subserosal or submucosal collections of blood In this respect, i e the escape to the surface of blood purpura of a serous surface or mucous membrane differs from purpura of the skin

Purpura however at times is more complicated than has just been described for exudation into serosa or mucous membrane may be mingled with simple hemorrhage and there may be an accompanying hyperemia In these events besides escape of red blood cells into the tissues serum inflammatory cells and fibrin may make their appearance in the lesions with accompanying hyperemia so that the resultant lesions may be not only hemorrhagic but erythematous or exudative or any

and below it to form a red thrombus In a vein the red thrombus attached at first only to the sticky platelets comprising the white thrombus may become dislodged as an embolus especially after its retraction Endothelial wettability may facilitate the latter process (Moolten and associates[4])

This is not the place to discuss in great detail the mechanism of clot formation and hemostasis those interested in knowing more about them are referred to the publications of the numerous investigators of these problems such as Alexander[1, 3] Fantl[4] MacFarlane[5] Mertz[6] Murphy[7] Owen[9] Quick[5, 1, 13] Seegers[7, 8, 6, 8, 3] Tocantins[11] Ware[8, 6, 8] M B Zucker[89] and H D Zucker[7]

For the purposes of this discussion of Purpura and Purpuric States the somewhat categorical statements in the preceding paragraphs will suffice In them are stated the many factors that play a part in stopping traumatic bleeding or causing hemostasis A disturbance in any one or a group of these will cause pathological bleeding or purpura and purpuric states These preceding paragraphs have given a bird s eye view of the numerous mechanisms which when disturbed may cause various types of pathological bleeding and form the basis of the classifications of the purpuras and purpuric states and the descriptions of them which follow

Procedures in Study of Patients with Purpura or Purpuric States

A careful history and complete physical examination of each patient with purpura or purpuric state should constitute the first step in the study this never should be neglected however illuminating special studies may be expected to be In the history any and all incidents of bleeding slow to stop or of easy bruising which have occurred in the patient or in members of the patient s family immediate or remote must be inquired into and recorded in as much detail as is possible The construction of a family tree as complete as it can be made with notation of prolonged bleeding and/or easy bruising in any ancestor may be of great value in determining subsequently the type of bleeding disease which the patient has To obtain the needed information the patient and available members of the patient s family should be questioned closely as to incidents of familial and ancestral bleeding or bruising with definite questioning as to occurrence of epistaxis hemoptysis hematemesis melena, hematuria menorrhagia metrorrhagia

pressure rises in the surrounding tissue by reason of the escaping blood Vasoconstriction and retraction of these vessels also occur promptly, the former lasting for a few minutes or a longer period while retraction persists for a long time Commencing very shortly clot formation takes place both within and about the ruptured vessel from platelets adhering to the vessel surface and agglutinating to form platelet masses, soon followed by fibrin deposition to make firmer, and facilitate adhesion of the clot so that it plugs the ruptured vessel and stops the bleeding These several factors work together to stop bleeding a process still far from understood in all details of its mechanism

Until recently blood coagulation has been explained by the following schema[69]

Prothrombin + Calcium + Thromboplastin ——→ Thrombin
Thrombin + Fibrinogen ——→ Fibrin

However, other factors now are recognized and introducing these the following schema of blood coagulation may be constructed

Platelet Enzyme + Thromboplastinogen ——→ Thromboplastin
Thromboplastin + Prothrombin + Calcium ——→ Thrombin
Plasma Prothrombin Accelerators + Thrombin ——→ Serum Prothrombin Accelerators
Prothrombin + Serum Prothrombin Accelerators ——→ Thrombin
Thrombin + Fibrinogen ——→ Fibrin

Clotting is necessary to the formation of a thrombus firm enough to plug the bleeding vessel, i e , thrombosis The process of thrombosis has been summarized as follows[204]

1 The alteration of the endothelial lining even when not demonstrable histologically may render it more wettable and initiate thereby the local production of thrombin

2 'Platelets swept into contact with such altered endothelium adhere to it and are in turn further agglutinable by the lytic action of locally formed thrombin thereby entrapping other platelets in large numbers As their lysis proceeds to completion the agglutinated platelets *liberate accelerator substances which intensify the local production of thrombin If the blood flow is rapid* much of the *deposit of thrombin* and platelets is swept away If the current is relatively sluggish, platelets are deposited in rapidly mounting numbers until the lumen is totally occluded by white thrombus

3 'Continued elaboration of thrombin under the accelerating influence of platelet lysis en masse in the newly formed white thrombus quickly results in clotting of the entire column of stagnant blood above

counting the petechiae in a circle 5 cm in diameter drawn on the forearm . 5 cm below the antecubital fossa In the Dalldorf negative pressure test a negative pressure of oo mm Hg is maintained for 1 minute over a circular area 1 cm in diameter and the number of petechiae produced in this circle is to be counted

Bleeding time is to be obtained by making a stab wound 2 mm in length and depth in the dependent portion of the lobe of the ear with a sharp pointed scalpel At half minute intervals the accumulated blood is removed by touching it but not the skin with a piece of filter paper The end point is failure of blood to appear on the filter paper the time taken for this to happen is the bleeding time It is advisible not to determine bleeding time in patients with hemophilia or with afibrinogenemia, since in these patients although bleeding time is normal very often later the puncture begins to ooze and this may be very difficult to stop The mean normal bleeding time is 3 2 seconds

Platelet counts are to be made by any of the accepted methods *Clot retraction* or *syneresis* is determined by placing c c of blood freshly obtained by vein puncture in a thoroughly cleaned and dry test tube which is put in a water bath at 37 . C and observed after ½, 1 2 4 and 4 hours for signs of retraction namely the separation of clot with expression of serum In addition as a semiquantitation the fluid volume occluded within the clot can be determined by a method devised by Aggeler, Lucia and Hamlin [9, 92]

Measurement of coagulation or clotting time of venous blood can be made by a modified Lee White method in which with the least possible stasis and every precaution against trauma venous blood is obtained in a syringe which has been thoroughly cleansed and rinsed with normal saline solution just before using this blood is to be placed carefully in c c amount in two chemically cleaned test tubes previously rinsed twice with normal saline and the tubes put in a water bath at ,7 5°C At intervals of one minute one of the tubes is observed for clotting by removal from the bath and gently tilting The end point or clotting time is when the tube can be inverted without loss of contents the time elapsed being measured from the time when the blood first enters the syringe The second tube then is tested as just described as a control The normal of clotting time by this method ranges between 4 and 1 minutes

Clotting time of recalcified plasma (recalcification time) can be measured as follows A sample of 4 5 c c of venous blood is mixed with 0 5 c c of 0 1 molar solution of potassium oxalate and this is centrifuged

all questioning being expressed in words easily understandable by a lay person, about possible prolonged bleeding after tooth extractions or other minor surgical procedures and about the occurrence of arthralgia and arthritis suggestive of joint effusions or of hemoarthrosis, the individuals being questioned should be asked at what age these disturbances appeared, how long they lasted and how often they occurred. Direct questioning often recalls bleeding events forgotten by the patient who has been allowed to give his history without such guidance and stimulation as has just been indicated. It may well be helpful to ask about black and blue marks, some of which the patient may not have associated with bruising.

The patient's history should include query and notation of the taking of any drug or of any infectious process prior to the incidence of bleeding or easy bruising. A careful dietary history is to be obtained in search for a possible food deficiency or food idiosyncrasy or food allergy. Symptoms indicative of an allergy or the existence of a prior anemia should be explored very thoroughly.

In the physical examination, along with the usual observations, special search should be made for the presence of any telangiectases in skin and/or mucous membranes that can be visualized by direct and instrumental inspection. Signs of present or previous bleedings in brain, joints, muscles and subcutaneous tissue should be recorded. Enlargement of lymph nodes and of spleen should be looked for, aided by x-ray to reveal enlarged mediastinal nodes and splenic enlargement not detectable by palpation. The urine should be examined for albumin, casts and especially for red blood cells. The primary blood study should include count of red and white cells and platelets, hemoglobin estimation and study of stained smear with attention to details of cytology and relative distribution and proportion of red cells, white cells and platelets.

All of these queries and examinations should precede the special studies now to be described.

Special Studies.—An index of *capillary fragility* is to be obtained by the tourniquet (Rumpel-Leede test) or negative pressure test (Dalldorf method[91]). In the former a blood pressure cuff is applied to the upper arm and the pressure in it raised for 10 minutes to 100 mm. Hg, unless the patient's systolic pressure is less than 100. If so, the cuff pressure should be midway between the patient's systolic and diastolic blood pressure. After 10 minutes' application the blood pressure cuff is to be removed and 5 minutes later search made for petechiae. Some qualitative results for comparison with other patients may be obtained by

counting the petechiae in a circle 5 cm in diameter drawn on the forearm 2 5 cm below the antecubital fossa In the Dalldorf negative pressure test a negative pressure of 200 mm Hg is maintained for 1 minute over a circular area 1 cm in diameter and the number of petechiae produced in this circle is to be counted

Bleeding time is to be obtained by making a stab wound 2 mm in length and depth in the dependent portion of the lobe of the ear with a sharp pointed scalpel At half minute intervals the accumulated blood is removed by touching it but not the skin with a piece of filter paper The end point is failure of blood to appear on the filter paper the time taken for this to happen is the bleeding time It is advisable not to determine bleeding time in patients with hemophilia or with afibrinogenemia since in these patients, although bleeding time is normal very often later the puncture begins to ooze and this may be very difficult to stop The mean normal bleeding time is 3 seconds

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Measurement of coagulation or clotting time of venous blood can be made by a modified Lee White method in which with the least possible stasis and every precaution against trauma venous blood is obtained in a syringe *which has been thoroughly cleansed and rinsed with normal* saline solution just before using this blood is to be placed carefully in c c amount in two chemically cleaned test tubes previously rinsed twice with normal saline and the tubes put in a water bath at 37 5 C At intervals of one minute one of the tubes is observed for clotting by removal from the bath and gently tilting The end point or clotting time is when the tube can be inverted without loss of contents the time elapsed being measured from the time when the blood first enters the syringe The second tube then is tested as just described as a control The normal of clotting time by this method ranges between 4 and 1 minutes

Clotting time of recalcified plasma (recalcification time) can be measured as follows A sample of 4 5 c c of venous blood is mixed with 0 5 c c of 0 1 molar solution of potassium oxalate and this is centrifuged

at 1,000 r.p.m. for 5 minutes. Then 0.1 c.c. of this plasma is added to a 10 by 75 mm. lipless test tube; this is placed in a water bath at 37.5 C. To it is added 0.2 c.c. of 0.025 molar calcium chloride solution, a stop watch is started, and contents of tube are gently mixed. The tube is observed for coagulation at 60 seconds and every 15 seconds thereafter, the tube being kept in water bath and agitated as little as possible. The end point is complete coagulation of plasma, the normal time being 90 to 120 minutes. This is prolonged in thrombocytopenia, parahemophilia and afibrinogenemia but not in scurvy or thrombasthenia.

Screening tests for abnormal coagulation can be carried out as follows. By simultaneous venous puncture, using cleaned syringes and needles rinsed with sterile saline solution, 10 c.c. of venous blood is withdrawn with stop watch timing from patient suspected of abnormal coagulation and from a normal control. Mixtures of the two then are made in six test tubes using 2.0, 1.6, 1.2, 0.8, 0.4, 0.01 c.c. of patient's blood and decreasing amounts from 0 to 2 c.c. of blood of normal control. Coagulation time then is determined for whole blood and for these tubes of serially mixed blood. In the way already described in the preceding paragraph similar mixtures are made of oxalated plasma of patient and of control, and the coagulation times of recalcified mixtures and of plasma of each individual are determined. From these observations deficiency of a plasma factor or the presence of a circulating anticoagulant will be indicated. Then various special procedures can be carried out for the more specific identification of the nature of the deficiency factor and circulating anticoagulant.

The factor measured in determination of *prothrombin activity* is the speed of conversion of prothrombin to thrombin when optimal amounts of thromboplastin and calcium are added to citrated plasma. The thromboplastin is made from lyophilized rabbit brain that has been extracted with acetone. To 0.1 c.c. of thromboplastin solution in a standard test tube kept in a water bath at 37.5 C., 0.1 c.c. of citrated plasma is added and the tube is shaken gently. Timing with a stop watch, to this is added 0.1 c.c. of 0.25 molar solution of calcium chloride and gently mixed. The tube is taken out of water bath at about time clotting is anticipated, held in a horizontal position and gently moved back and forth. When the plasma in the tube no longer is fluid (i.e. has clotted) this is the end point and its time in seconds is noted and recorded as the prothrombin time. With this from a table giving the curve of prothrombin time concentration this value can be determined in terms of percentage of normal. Since the first part of

such a curve is so steep that slight differences in prothrombin time make great differences in concentration a method of dilution with prothrombin free plasma makes possible greater accuracy in reading prothrombin concentration Prothrombin free plasma is prepared by using the absorbing property of barium sulfate for prothrombin

Prothrombin consumption, i e the amount of prothrombin not utilized in the clotting process can be estimated also and this gives additional evidence about the clotting process and presence or absence of *prothrombin accelerators*[30, 303]

The determination of *fibrinolysin* (*plasmin*) a proteolytic enzyme has importance because it can alter coagulation in several ways coagulation may be normal with subsequent partial lysis of the clot it may be normal with subsequent complete lysis of the clot there may be no coagulation because of rapid fibrinogenolysis and resultant afibrinogenemia Fibrinolytic activity can be measured by observation of the stability of whole blood or of recalcified plasma Coagulation time as already outlined is determined and recorded After it has occurred the tube is left in the water bath at 37 5 C and observed for dissolution of the clot at half an hour one two three four and twenty four hours If fibrinolysin is present the clot will be observed to decrease in size with loss of many of its red cells Ac globulin is readily destroyed by fibrinolysin but prothrombin and thromboplastin apparently are not affected by this lysin while thrombin might be destroyed slowly by it[304]

CLASSIFICATION

The most satisfactory classifications that I have seen is that of Leschke[1] as somewhat modified by Pratt[3] adopting the term anaphylactoid as suggested by Pfaundler Frank[4] and Glanzmann which I used in the previous edition of this chapter and the recent one of Sturgis[1] which follows

Sturgis [10] Classification of the Hemorrhagic States

1 Hemorrhagic states due to a decrease in the number of blood platelets (thrombopenic purpura)

A Idiopathic thrombopenic purpura (purpura hemorrhagica)

at 1,000 r p m for 5 minutes Then 0 1 c c of this plasma is added to a 10 by 75 mm lipless test tube, this is placed in a water bath at 37 5 C To it is added 0 2 c c of 0 025 molar calcium chloride solution, a stop watch is started, and contents of tube are gently mixed The tube is observed for coagulation at 60 seconds and every 15 seconds thereafter, the tube being kept in water bath and agitated as little as possible The end point is complete coagulation of plasma, the normal time being 90 to 120 minutes This is prolonged in thrombocytopenia, parahemophilia and afibrinogenemia but not in scurvy or thrombasthenia

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CLASSIFICATION

The most satisfactory classifications that I have seen is that of Leschke[1] as somewhat modified by Pratt[2] adopting the term anaphylactoid as suggested by Pfaundler, Frank[4] and Glanzmann, which I used in the previous edition of this chapter, and the recent one of Sturgis[12] which follows.

Sturgis' Classification of the Hemorrhagic States

I *Hemorrhagic states due to a decrease in the number of blood platelets (thrombopenic purpura)*

A Idiopathic thrombopenic purpura (purpura hemorrhagica)

B Symptomatic thrombopenic purpura

1 In association with blood diseases
   (a) Leukemia
   (b) Aplastic anemia
   (c) Pernicious anemia
   (d) Sickle cell anemia
   (e) Hemolytic anemia
   (f) Banti's disease
   (g) Gaucher's syndrome
   (h) Felty's syndrome

2 Infections
   (a) Typhoid fever
   (b) Meningococcus infections
   (c) Upper respiratory infections
   (d) Septicemia
   (e) Typhus fever
   (f) Miliary tuberculosis
   (g) Small pox
   (h) Vaccinia
   (i) Lupus erythematosus
   (j) Subacute bacterial endocarditis

3 Cancer (bone marrow metastases)
   (a) Cancer of the stomach
   (b) Multiple myeloma
   (c) Any malignant neoplasm which may metastasize to bone marrow

4 In cirrhosis of liver

5 Allergic thrombopenia
   (a) Drug allergy
      (1) Organic arsenicals (arsphenamine etc)
      (2) Sedormid
      (3) Gold preparations
      (4) Benzol
      (5) Sulfonamide drugs
      (6) Quinine
      (7) Possibly ergot, bismuth phenobarbital iodides and others
   (b) Food allergy

II Hemorrhagic states due to changes in the capillary walls (non thrombopenic purpura)
- A Infectious diseases
  1. Endocarditis
  2. Typhus fever
  3. Meningitis
  4. Septicemia
  5. Pneumonia
  6. Typhoid fever
  7. Tuberculosis
  8. Chronic infections such as pyelonephrosis lung abscess etc
  9. Scarlet fever
  10. Waterhouse Friederichsen syndrome
- B Toxins of nephritic origin
- C Schonlein Henoch s purpura (anaphylactoid)
- D Drug and food sensitivity
- E Vitamin deficiency
  1. Vitamin C deficiency (scurvy)
  2. Vitamin P deficiency
- F Abnormal capillary fragility in the new born
- G Hereditary familial purpura simplex

III Hemorrhagic states due to changes in the normal clotting elements of the blood
- A Deficiency of prothrombin
  1. Due to dietary defects of vitamin K
     - (a) Hemorrhagic disease of the new born
     - (b) Dietary defects in the adult
  2. Faulty absorption of vitamin K
     - (a) Jaundice and bile fistula
     - (b) Sprue
     - (c) Chronic ulcerative colitis and other chronic intestinal conditions
  3. Impaired formation of prothrombin by the liver
     - (a) Cirrhosis of the liver
     - (b) Banti s disease
     - (c) Felty s syndrome
     - (d) Acute yellow atrophy
     - (e) Chloroform carbon tetrachloride and phosphorus poisoning

B Symptomatic thrombopenic purpura
- 1 In association with blood diseases
  - (a) Leukemia
  - (b) Aplastic anemia
  - (c) Pernicious anemia
  - (d) Sickle cell anemia
  - (e) Hemolytic anemia
  - (f) Banti's disease
  - (g) Gaucher's syndrome
  - (h) Felty's syndrome
- 2 Infections
  - (a) Typhoid fever
  - (b) Meningococcus infections
  - (c) Upper respiratory infections
  - (d) Septicemia
  - (e) Typhus fever
  - (f) Miliary tuberculosis
  - (g) Small pox
  - (h) Vaccinia
  - (i) Lupus erythematosus
  - (j) Subacute bacterial endocarditis
- 3 Cancer (bone marrow metastases)
  - (a) Cancer of the stomach
  - (b) Multiple myeloma
  - (c) Any malignant neoplasm which may metastasize to bone marrow
- 4 In cirrhosis of liver
- 5 Allergic thrombopenia
  - (a) Drug allergy
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    - (c) Felty s syndrome
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    - (e) Chloroform carbon tetrachloride and phosphorus poisoning

4 Inactivation of prothrombin (dicoumarin)
5 Idiopathic prothrombinemia
B Abnormal bleeding due to qualitative changes in the platelets
1 Hemophilia due to a decreased amount of thromboplastin
2 Chronic hereditary thrombasthenia
C Fibrinogen deficiency
1 Acquired fibrinogenopenia (nutritional disturbances, phosphorus poisoning, severe liver damage)
2 Congenital fibrinogenopenia (pseudohemophilia)
D Circulating anticoagulants
1 Liberation of heparin in the blood
(a) Peptone shock
(b) Anaphylactic shock
2 Excessive antithrombin

These classifications I have used as the basis of one which has been simplified and changed somewhat to fit the purposes of this chapter In that form it follows herewith

1 Thrombocytopenic Purpura
A Essential Primary or Idiopathic
1 Common Forms
(a) Marrow Aplasia
(b) Hypersplenism
2 Special Forms
(a) Cyclic Thrombocytopenic Purpura
(b) Thrombocytopenic Purpura with Generalized Platelet Vasothromboses
B Secondary or Symptomatic
(a) In blood diseases
(b) In other diseases with certain disturbances in the blood and/or the bone marrow
(c) Infections and infectious diseases
(d) Intoxications including drug idiosyncrasies
(e) Allergy
(f) Avitaminosis
(g) Radiation
2 Non thrombocytopenic Purpura
A Essential Primary or Idiopathic
(a) Anaphylactoid Purpura
(b) Purpura Simplex

(c) Purpura Senilis
(d) Purpura Cachectica
(e) Mechanical (Orthostatic) Purpura
B Secondary or Symptomatic
(a) Infections and infectious diseases
(b) Intoxications and drug idiosyncrasies
(c) Various chronic diseases
(d) Endocrine and nervous diseases
(e) Allergy
(f) Avitaminosis
3 Purpura Fulminans
4 Familial and Hereditary Purpura and Bleedings
A Hemophilia (antihemophilic globulin deficiency) (see Chapt XX Vol II of Oxford Medicine)
B Pseudohemophilia
C Recurrent Hemorrhage
(a) Epistaxis
(b) Hemoptysis
(c) Hematemesis
(d) Melena
(e) Hematuria
(f) Menorrhagia
D Hereditary Familial Purpura Simplex
5 Fibrinopenia
6 Hypoprothrombinemia
7 Hyperheparinemia
8 Circulating Non heparin Anticoagulants

It is recognized that in this classification overlapping in items of the subdivisions undoubtedly occurs and that others well might prefer to shift some sub headings from one group to another To me the most important service of this classification will be to give a bird s eye view of the entire group of purpura and the purpuric states before a detailed discussion of them is undertaken in subsequent pages of this chapter in which the sequence of arrangement will be that of the classification just given

The most important criteria on which the preceding classification is based are changes in the blood bone marrow plasma and capillaries Changes in the blood are made out by counts of platelets leucocytes and red cells by determinations of bleeding prothrombin and coagulation times by observation of retractility of blood clot and by study of

blood smears with particular attention to the number appearance and grouping of platelets, changes in the bone marrow are made out by study and counts of its component cells as observed in fresh and stained smears from material obtained by sternal puncture Plasma needs to be studied for content of fibrin, prothrombin globulin accelerator heparin or other circulating anticoagulants etc Capillaries should be studied for fragility, contractility, presence of thrombi etc When these various observations have been made and then only, are we in a position to place accurately any observed patient in the classification Until this has been done a correct diagnosis followed by suitable proceedures in treatment is not probable

THROMBOCYTOPENIC PURPURA (PURPURA HEMORRHAGICA)

Introduction

Synonyms—Werlhof's disease morbus maculosus haemorrhagicus of Werlhof thrombopenic purpura thrombopenia thrombocytolytic purpura purpura thrombogenia hemogenia, hemogenic syndrome

Definition—Thrombocytopenic purpura may be defined as a condition with the following main characteristics the occurrence of petechiae macules or larger ecchymoses or extravasations a reduced platelet count a prolonged bleeding time and a non retractile clot In some cases hemorrhage occurs from mucous membranes without the presence of skin lesions or the reverse may be true, often both are present The usual skin lesion is a simple hemorrhage into the skin not an hemorrhagic, exudative process with accompanying erythema and swelling Thrombocytopenic purpura is of two kinds *essential, primary* or *idiopathic thrombocytopenic purpura* and *secondary* or *symptomatic thrombocytopenic purpura*

Etiology and Incidence of Thrombocytopenic Purpura

The primal etiology of essential primary or idiopathic thrombocytopenic purpura is not known Rarely heredity plays some role in it Some believe it an allergic phenomenon The etiology of secondary or

symptomatic purpura is various as has been indicated in the classification on a previous page where the several causes are used as subdivisions or subheadings in the classification These will be enumerated in more detail when this form of thrombocytopenic purpura is discussed later in this chapter

Incidence of thrombocytopenic purpura is greatest in young adults but it may appear at any age from the cradle to the grave There may be definite heredity in its incidence Females are affected more often than males by the essential form while the reverse tends to be true of secondary or symptomatic thrombocytopenic purpura

Pathological Physiology and Pathology of Thrombocytopenic Purpura

The most significant change in patients with thrombocytopenic purpura is the decrease in the number of thrombocytes or platelets in the blood *to a point where no longer do they carry out their normal* function in the mechanism of the clotting of blood to stop bleeding and/or evidence of hypersplenism the *thrombocytopenic factor* In addition to this as in other forms of purpura the walls of small blood vessels appear to have become more vulnerable to minor injuries and more permeable than is normal This is an additional causative factor in the mechanism of thrombocytopenic purpura the *vascular vulnerability factor* Thus there are two factors the thrombocytopenic factor with or without hypersplenism and the vascular vulnerability factor which are concerned in the development of the lesions of thrombocytopenic purpura

Thrombocytopenic Factor

First I will consider the thrombocytopenic factor To understand this a knowledge of the histogenesis of platelets of the histology of the platelet and of its precursor cells and of the pathological physiology and pathology of the process is needed

The Thrombocyte or Platelet and the Megacaryocyte —The thrombocyte or platelet as shown 45 years ago by *J Homer Wright of Boston*[1] *is formed in the bone marrow by a pinching off of the granular* cytoplasm of megacaryocytes Wright's observations have had the

confirmation of many others (Bunting[9, 13], Smith, Robinson and Tyson[14], Weiskotten, Wyatt and Gibbs[15], Bedson and Johnston[16], Firket and Campos[17], Volterra[18]), and this histogenesis of the platelet now seems acceptable to almost all investigators of the subject

The question however, naturally arises, is this the only source of blood platelets under all conditions of increased demand on platelet formation Probably it is not the only source W H Brown[8] (1913) described platelet production from monocytes as occurring under excessive demand Bunting[9] (1920) claimed that platelets or platelet like bodies were formed from lymphocytes in the blood stream in the thrombocytopenia of some patients with epidemic influenza Howell and Donahue[10] (1937) concluded that new platelets could be added to the blood in capillary areas of the lungs With myeloid metaplasia in spleen, lung and other sites megacaryocytes develop elsewhere than in the bone marrow and in these places can form platelets[29, 30, 31] Tocantins[11] has reviewed this subject carefully, for further information the reader is referred to his monograph However, the megacaryocytic origin of platelets chiefly if not solely, in the bone marrow fits admirably with present day views as to the mechanism of thrombocytopenic purpura

According to Dameshek and Miller[2] the following cells of the megacaryocyte series can be recognized in smears of the bone marrow (1) megacaryoblasts which do not produce platelets normally or in essential thrombocytopenic purpura they comprise less than 1 per cent of all the megacaryocytes, (2) promegacaryocytes which frequently have platelet-like bodies at the periphery of their cytoplasm and rarely under normal conditions but frequently in cases of purpura have non granular cytoplasmic processes these make up about one third of the total number of megacaryocytes and form platelets, (3) lymphoid megacaryocytes a few of which appear to form platelets (4) intermediate forms which may or may not form platelets, (5) adult megacaryocytes with typical granular platelets frequently grouped in masses about the periphery of the cells they actively form platelets (6) prepolycaryocytes, which are not increased in purpura, (7) polycaryocytes probably fused syncytia of prepolycaryocytes from which by nuclear fusion probably also adult megacaryocytes are formed and these in turn produce platelets, (8) degenerated forms some of which may still be forming platelets According to Dameshek and Miller[1] the numerical relationships of these various types of cells to each other as seen in bone marrow smears may be more artificial than real Because of

this uncertainty they designate megacaryoblasts and promegacaryocytes as "young forms" and the lymphoid megacaryocytes intermediate forms and adult types as "adult forms" with a separate designation for the degenerated cells

Dameshek and Miller[12] believe that the predominant mode of origin of the megacaryocyte in the bone marrow probably is from a stem cell or megacaryoblast which in turn probably originates from the pluripotential histiocyte or hemohistioblast to this many agree A subsidiary method of origin seems to be from the polycaryocyte or osteoclast Di Guglielmo[13] believes that the polycaryocyte is derived from the fusion of primitive mononuclear histoid cells with the resultant development of large multinucleated giant cells which in turn become megacaryocytes agreement to this is not general, although other observers agree to it

Megacaryocytes under certain conditions may develop too outside the bone marrow as from non phagocytic fixed tissue cells lining the sinusoids of the liver (Bloom) from reticulum and myeloblasts (Downey Palmer and Powell[1]) and from myeloblasts in the peripheral blood and hemocytoblasts in the spleen (Downey and Nordland)

In the bone marrow of 10 normal patients Dameshek and Miller[1] found the following features (1) not more than 300 megacaryocytes per million nucleated cells were present (2) about two thirds of the megacaryocytes showed platelets or platelet-like bodies at the periphery of their cytoplasm (3) megacaryoblasts were rare (4) promegacaryocytes usually producing granular platelets were plentiful Non granular platelet production was rare Approximately one half of the platelet producing megacaryocytes were young forms (5) degenerated forms varied from 8 to [illegible]2 per cent of all cells

The platelet is a non nucleated body usually of small size [illegible] to 4 microns as compared with other blood cells much larger forms do occur They have a granular cytoplasm with a narrow clear peripheral zone Their shape in general is circular with slightly irregular edges but they may be oval or of bizarre shapes Their number varies from 50 000 to 900 000 per cubic millimeter of blood depending somewhat on the method used in their enumeration[3] It is well in counting platelets always to make a simultaneous count from the blood of a known normal as a control on the technic of counting this author always has insisted on this as a check on the work of the technician using necessarily a method which is subject to unavoidable occasional and unpredictable variations in results

The Platelet in the Circulating Blood—Platelets formed in the bone marrow normally make their way, without further morphological change, into bone marrow vascular channels to reach the circulating blood The exact mechanism of this is not known Some believe that the megacaryocyte's pseudopod, the tip of which pinches off to form the platelet, protrudes into the vascular channel and sets free from its tip the newly formed platelet Others think that the platelet freed in the interstices of the bone marrow wander into the blood channels by some unknown mechanism After reaching the blood stream the platelets survive for only four or five days, but the exact mechanism of their disappearance is not known Some believe that, being fragile anyhow, they simply *gradually disintegrate in the circulating* blood and disappear Others think that, having a strong tendency to adhere to any surface they adhere singly or in small groups to the lining of very small blood vessels where blood flow is slow and there disintegrate and disappear Still others think that this latter process leads to the formation of small thrombi into which the circulating platelets disappear, this does not seem very probable as a normal mechanism but it does occur extensively under certain pathological conditions to be described later in this chapter Some believe that so-called sludging of the blood[48] at times has a part in the fate of platelets Finally some believe that the disappearance of platelets from the circulating blood is by phagocytosis by various body cells particularly by cells of the reticulo endothelial system and that this occurs most extensively in the spleen[9] Of this there is evidence in various studies of pathological conditions by Doan and his associates[8, 9, 30] and others Possibly not one but several of these possible mechanisms bring about the normal disappearance from the circulation of the platelets

Role of the Spleen (Hypersplenism) —The role of the spleen in the formation of platelets and their decrease in certain pathological conditions although far from being thoroughly understood seems to be definitely important[18, 36] A most striking evidence of such influence of the spleen is to be found in the effects of splenectomy in normal individuals and in patients with essential thrombocytopenic purpura In the latter removal of the spleen is followed promptly by an increase in the blood of normal appearing platelets[1, 27, 28, 9, 30, 4, 43, 44, 45, 46, 47]

Splenic influence on platelet production is seen also in the not infrequent development of thrombocytopenia in patients with various types of splenomegaly as in cirrhosis of the liver splenic vein thrombosis Gaucher's disease sarcoid of the spleen splenic amyloidosis, leukemia

lymphomatosis Hodgkin's disease Felty's syndrome etc and its amelioration following splenectomy[1] [5] Were there needed additional evidence of this it can be found in those patients in whom a return of thrombocytopenia following splenectomy has been followed by its second disappearance subsequent to removal of an accessory spleen or several such spleens[30] [41]

This controlling action of the spleen on platelet formation in the bone marrow can be thought of as hormonic or endocrinic Some claim that it is under pituitary control At any rate it seems definitely a remote action of the spleen mediated in some way to the bone marrow and its megacaryocytes When it is marked some call it *hypersplenism*[6] [96] From spleens removed from patients with thrombocytopenic purpura there has been extracted a substance or substances called either splenin[10] or thrombocytopen[1] [31] [3] [32] which when injected into animals has an effect on platelet production sometimes but not always decreasing the number of platelets in the circulation this being further evidence of the so-called hormonic action of the spleen in inhibiting platelet production through some substance carried in the circulation from the spleen to the bone marrow[1] [31] [3] [34] All however are not in agreement as to this so called hormonic action of the spleen believing that in idiopathic thrombocytopenic purpura the spleen decreases the platelets in the circulation by phagocytosis of them in the spleen by macrophages[8] and not by some effect on the mechanism of platelet production in the bone marrow

However whichever view is held as to the mechanism it seems clear that the spleen influences the number of platelets in the circulation leading to their marked decrease in essential or idiopathic thrombocytopenic purpura a condition strikingly reversed by splenectomy

In this latter sense the spleen is not normal in essential thrombocytopenic purpura although according to some the spleen may show no histological departure from normal in other words its abnormality in these patients is functional not structural In some of the patients the spleen is normal in size in others it is enlarged showing either simple hyperplasia or in secondary or symptomatic thrombocytopenic purpura the presence of various conditions which are contributory to the causation of this form of thrombocytopenic purpura According to some the spleen is abnormal in thrombocytopenic purpura in the demonstrable presence of active phagocytosis of platelets Two schools of thought have developed in these respects the role of the spleen in the phagocytosis of platelets advocated by Dorn his associates and others with

The Platelet in the Circulating Blood.—Platelets formed in the bone marrow normally make their way, without further morphological change, into bone marrow vascular channels to reach the circulating blood. The exact mechanism of this is not known. Some believe that the megakaryocyte's pseudopod, the tip of which pinches off to form the platelet, protrudes into the vascular channel and sets free from its tip the newly formed platelet. Others think that the platelet freed in the interstices of the bone marrow wander into the blood channels by some unknown mechanism. After reaching the blood stream the platelets survive for only four or five days, but the exact mechanism of their disappearance is not known. Some believe that being fragile anyhow they simply gradually disintegrate in the circulating blood and disappear. Others think that, having a strong tendency to adhere to any surface they adhere singly or in small groups to the lining of very small blood vessels, where blood flow is slow, and there disintegrate and disappear. Still others think that this latter process leads to the formation of small thrombi into which the circulating platelets disappear, this does not seem very probable as a normal mechanism, but it does occur extensively under certain pathological conditions to be described later in this chapter. Some believe that so-called sludging of the blood[19] at times has a part in the fate of platelets. Finally, some believe that the disappearance of platelets from the circulating blood is by phagocytosis by various body cells particularly by cells of the reticulo-endothelial system, and that this occurs most extensively in the spleen.[9] *Of this there is evidence in various studies of pathological* conditions by Dorn and his associates[9, 9, 30] and others. Possibly not one but several of these possible mechanisms bring about the normal disappearance from the circulation of the platelets.

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the other view of an influence on platelet production in the bone marrow held by Dameshek, his associates and other students [49, 53, 18] of the subject

A subcutaneous injection of 0 5 to 1 c c of adrenalin (epinephrin) is utilized as a test for the existence of hypersplenism If positive this test (the adrenalin test) will reveal a hypersequestration of platelets indicative of a primary specific withdrawal of circulation platelets A platelet count following the epinephrin injection, if there exists hyper splenism, will show a decrease in the number of platelets which were present in the circulating blood prior to this injection of epinephrin

Robson[300] has studied changes in bleeding time capillary resistance and platelet counts before during and after splenectomy in both patients with thrombocytopenic purpura and patients without thrombocytopenic purpura in whom splenectomy was carried out in the treatment of various conditions other than purpura He found a sequence of changes in bleeding time capillary resistance and platelet counts after splen ectomy in patients with thrombocytopenic purpura which resulted in decrease in capillary bleeding increase in the number of the platelets and decrease in bleeding time In the control group i e individuals without purpura he found that these same changes followed splen ectomy often even more rapidly than in patients with thrombocytopenic purpura Similar changes followed operative procedures without the inclusion of removal of the spleen He thought that changes were brought about by a non-specific effect of operative intervention fol lowed by the effect of the removal of the spleen itself To him it was suggested from these observations that the cause of idiopathic thrombo penic purpura lies in the production by the spleen and other reticulo endothelial tissue of some factor which alters the state of capillaries i e reduces their resistance and also reduces platelet formation from megacaryocytes, and that removal of the spleen may bring about a complete or partial reversal of these effects

Other Pathological Changes — In addition to the changes already described in the bone marrow and spleen and the presence of focal hemorrhages with certain consequent effects in thrombocytopenic purpura with hemorrhages extensive enough to cause prolonged and marked anemia the body tissues especially the bone marrow and spleen will show changes caused by the incidental anemia In these the bone marrow will show the changes of an active erythropoiesis sometimes of leucopoiesis and rarely the changes of an aplastic anemia although

most usually the bone marrow is hyperplastic In some patients with thrombocytopenia there is a coincident leucopenia or neutropenia and/or anemia[7] in which all tissues concerned in hematopoiesis may show departures from normal or all elements of the blood may be reduced in number to constitute a panhematopenia

Possible Mechanisms of Platelet Decrease in the Blood — Theoretically a decrease in the number of platelets a thrombocytopenia could result from 1) inhibition of platelet formation in the bone marrow by megacaryocytes the megacaryocytes remaining normal in appearance and normal or increased in number, 2) failure of some of the megacaryocytes to go through normal maturation to the stage of platelet formation with a consequent decrease in number of platelets formed 3) pathological changes in the megacaryocytes with evidences of degeneration in them resulting in decreased formation of platelets 4) decrease in the number of megacaryocytes with consequent decreased formation of platelets 5) formation by normal or abnormal megacaryocytes of platelets either abnormal in appearance or abnormally fragile which either remain to disintegrate in the bone marrow or reaching the circulating blood either disappear with great rapidity or fail to function there in the normal way 6) failure of platelets normally formed in the bone marrow in normal numbers by megacaryocytes of normal structure to leave the bone marrow to get into the circulating blood 7) rapid destruction of normal platelets in the circulating blood after they reach it, 8) removal of platelets from the circulating blood by phagocytosis by cells in the blood stream or in the tissues such as those of the spleen 9) decrease in platelets in the circulating blood as result of extensive intravascular thrombosis thrombi being composed very largely of platelets

Obviously there could be overlaps between different ones of these theoretically possible mechanisms of decrease in platelets in the circulating blood with several mechanisms simultaneously in action However it is probable that some one of these mechanisms is dominant in each patient with thrombocytopenic purpura but it does not follow that in every patient the same mechanism is evident The latter allows for the possibility of not a single form but several forms of thrombocytopenic purpura depending on which mechanism to reduce the number of platelets in the circulating blood is in effect in the particular patient as will appear later on in this discussion

What evidence do we possess that any one of these theoretical causes of platelet decrease in number in the circulating blood occurs in

the other view of an influence on platelet production in the bone marrow held by Dameshek, his associates and other students[3, 49, 53, 88] of the subject

A subcutaneous injection of 0 5 to 1 c c of adrenalin (epinephrin) is utilized as a test for the existence of hypersplenism If positive, this test (the adrenalin test) will reveal a hypersequestration of platelets indicative of a primary specific withdrawal of circulation platelets A platelet count following the epinephrin injection if there exists hypersplenism will show a decrease in the number of platelets which were present in the circulating blood prior to this injection of epinephrin

Robson[303] has studied changes in bleeding time capillary resistance and platelet counts before during and after splenectomy in both patients with thrombocytopenic purpura and patients without thrombocytopenic purpura in whom splenectomy was carried out in the treatment of various conditions other than purpura He found a sequence of changes in bleeding time capillary resistance and platelet counts after splenectomy in patients with thrombocytopenic purpura which resulted in decrease in capillary bleeding increase in the number of the platelets and decrease in bleeding time In the control group i e individuals without purpura he found that these same changes followed splenectomy often even more rapidly than in patients with thrombocytopenic purpura Similar changes followed operative procedures without the inclusion of removal of the spleen He thought that changes were brought about by a non-specific effect of operative intervention followed by the effect of the removal of the spleen itself To him it was suggested from these observations that the cause of idiopathic thrombopenic purpura lies in the production by the spleen and other reticulo endothelial tissue of some factor which alters the state of capillaries i e reduces their resistance and also reduces platelet formation from megacaryocytes and that removal of the spleen may bring about a complete or partial reversal of these effects

Other Pathological Changes — In addition to the changes already described in the bone marrow and spleen and the presence of focal hemorrhages with certain consequent effects in thrombocytopenic purpura with hemorrhages extensive enough to cause prolonged and marked anemia the body tissues especially the bone marrow and spleen will show changes caused by the incidental anemia In these the bone marrow will show the changes of an active erythropoiesis sometimes of leucopoiesis and rarely, the changes of an aplastic anemia although

in the megacaryoblasts and by those of Fieschi and Billilobos[1] who found in a study of 8 patients a disturbance in the maturation of megacaryocytes with an increase in young forms and an asynchronism in the maturation of the nucleus and protoplasm Also certainly this is a possibility in thrombocytopenic purpura of toxic etiology but so far as I know no bone marrow examinations in such cases have shown this We may conclude however that theoretical cause (2) may be a contributory if not a chief mechanism in the production of platelet deficiency in the circulating blood

Pathological changes in the megacaryocytes, evidences of degeneration in them resulting in decreased formation of platelets theoretical cause (3) seems certainly a factor in the cause of secondary thrombocytopenic purpura where leucemia or neoplasm so crowds the bone marrow as to injure megacaryocytes Also various toxic substances probably similarly would injure and cause degenerative changes in megacaryocytes to inhibit formation of platelets by them Various authors have noted degenerative changes in megacaryocytes but do not consider them of any considerable importance in the mechanism of platelet decrease

If theoretical cause (2) continued presumably an *increasing diminution in the number of megacaryocytes* would take place This seems to have happened in the bone marrow of some patients with secondary thrombocytopenic purpura This is theoretical cause (4) for thrombocytopenic purpura Such a change was found by Dameshek and Miller[1] in cases of thrombocytopenic purpura developing in patients with the bone marrow lesions which are encountered in patients with aplastic anemia leucemia or lymphosarcoma Numerous older reports noted decrease in number of megacaryocytes in the bone marrow of patients with thrombocytopenic purpura but many possibly all of these may be explained by imperfections in technic of bone marrow examinations In contrast recent reports based on modern technics of intravitam bone marrow study have not shown these decreased numbers of megacaryocytes in the bone marrow It is possible that some subsequent study of bone marrow from cases of thrombocytopenic purpura may show a definite and considerable decrease in the number of megacaryocytes and differentiate from the usual type of thrombocytopenic purpura a particular form due chiefly to lack of megacaryocytes in sufficient number to maintain a normal level of platelets in the circulating blood

The formation of *platelets of abnormal appearance and/or of increased fragility* theoretical cause (5) is suggested by some observa

man with demonstrable platelet deficiency? This question can be answered most satisfactorily by considering in succession each of the theoretically possible causes numbered (1) to (9)

The existence of theoretical cause (1), *inhibition of platelet formation in the bone marrow by megacaryocytes*, the megacaryocytes remaining normal in appearance and normal or increased in number is supported first by numerous studies of bone marrow smears from patients with thrombocytopenic purpura which show a normal or increased number of normal appearing megacaryocytes, when platelets in the circulating blood are much decreased in number and second by finding in bone marrow smears a decreased number of megacaryocytes in the process of forming platelets, and third by the reappearance of active platelet formation by megacaryocytes following splenectomy *with corresponding increase in the number of platelets in the circulating* blood As an example of this Dameshek and Miller[1] found in the bone marrow of 5 cases of acute thrombocytopenic purpura that (1) the number of megacaryocytes per million nucleated red cells was on the average about three times greater than in the normal, and ( ) only 14 4 per cent of these megacaryocytes showed obvious platelet production as contrasted with normal cases in which approximately two thirds of the megacaryocytes were producing platelets In 4 of these cases following splenectomy platelet production by megacaryocytes became sharply increased from the average of 16 per cent before splenectomy to 73 per cent after it while the number of megacaryocytes per million nucleated red cells remained at about the same level or became somewhat increased in number Such an increase in megacaryocytes with decreased platelet production has been observed also by Seeliger[34] Minot[3] Gasper[50] Nickerson and Sunderland[1] Wemer and Kaznelson Limarzi and Schleicher[3] Valentine and others

A decrease in number of platelets in the circulating blood because of *failure of megacaryocytes to mature to the stage of platelet production*, theoretical cause (2) is a mechanism which could cause thrombocytopenic purpura If this process was going on then bone marrow smears would show a decreased number of more mature megacaryocytes and an increased number of the immature ones the megacaryoblasts and possibly the promegacaryocytes of the classification already cited from the work of Dameshek and Miller[1] That this mechanism plays some part in reduction of platelet formation is indicated by the studies of Dameshek and Miller[1] who found in the bone marrow of patients with acute and with chronic thrombocytopenic purpura a definite increase

in the megacaryoblasts and by those of Fieschi and Billalobos[44] who found in a study of 8 patients a disturbance in the maturation of megacaryocytes with an increase in young forms and an asynchronism in the maturation of the nucleus and protoplasm Also certainly this is a possibility in thrombocytopenic purpura of toxic etiology but so far as I know no bone marrow examinations in such cases have shown this We may conclude however that theoretical cause ( ) may be a contributory if not a chief mechanism in the production of platelet deficiency in the circulating blood

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tions, but definite proof that this is an important mechanism in patients with thrombocytopenic purpura is lacking Theoretical cause (6) *failure of normally formed, normally appearing platelets to leave the bone marrow,* is somewhat in the same category, i e lack of definite proof However, this would seem to be a possibly significant factor in some patients in whose bone marrow numerous, normally appearing platelets are seen in normal relation to normal appearing megacaryocytes Bone marrow studies by Dameshek and Miller[12] of 5 cases of so called hypersplenic thrombocytopenic purpura are consistent with this mechanism deficient delivery of platelets from the bone marrow to the circulating blood they having found in the bone marrow of patients with splenomegaly due to cirrhosis of the liver chronic infection Gaucher's disease Boeck's sarcoid and Felty's syndrome an increase in megacaryocytes with a normal degree of platelet production, they consider defective delivery the probable mechanism here, splenectomy in these patients quickly restored platelets to normal number in the circulating blood this being further evidence of that mechanism Of course the same findings would be present if platelets were decreased in the circulating blood because of their abnormal fragility and shortened life cycle theoretical cause 5

Theoretical cause (7), *rapid destruction of normal platelets in the circulating blood* after they reach it may be an occasional cause of thrombocytopenic purpura That such a process can occur is supported by animal experimentation in which an anti platelet serum is made by the injection of platelets and then, when this is injected into another animal platelet destruction takes place with changes very similar to those found in thrombocytopenic purpura The experiments of Lee and Robertson[56] LaSourd and Paginez[57], Hyde[9] and others show this possibility From the spleens of patients with thrombocytopenic purpura have been isolated substances which when injected into animals sometimes cause lysis of platelets with changes like those found in thrombocytopenic purpura[1, 31, 3, 33, 36, 37, 38] This is further evidence that a lytic process may be responsible for thrombocytopenic purpura Such a lytic process may be the mechanism in some human cases of thrombocytopenic purpura caused by toxic chemicals

Removal of platelets from the circulation by cellular phagocytosis, theoretical cause 8 is supported by the studies of Doan and his associates[7, 8, 9, 30], who have demonstrated such phagocytosis by cells in the spleen removed from cases of thrombocytopenic purpura They

believe that such phagocytosis is an important mechanism in the production of thrombocytopenic purpura

Removal of platelets from the circulating blood by extensive intravascular thrombosis, theoretical cause 9 appears to be the explanation of the development of thrombocytopenic purpura in certain patients as reported by Baehr Klemperer and Schifrin[80] Gitlow and Goldmark[1] Altschule[6] Bernheim[83] Trobaugh Markowitz Davidson and Crowley[85] Carter[8] Engel Scheinker and Humphrey[84] Gore and others This however is an unusual mechanism of thrombocytopenic purpura but it constitutes a definite clinical syndrome to be discussed later on in this chapter

Vascular Vulnerability Factor

As already referred to there seems to be in thrombocytopenic purpura something more than a platelet deficiency to explain the hemorrhages and various disturbances in the capillaries have been assumed They are definitely more vulnerable or more permeable than normal as shown by various tests which cause hemorrhages into the skin in this condition If a tourniquet is placed around the upper arm (the cuff of the blood pressure apparatus with the pressure blown up to a point intermediate between systolic and diastolic pressure is a convenient way to make this test) and allowed to remain for 10 to minutes the appearance of petechiae or ecchymoses in the forearm below the constricting band is an indication of lessened capillary resistance In thrombocytopenic purpura this test usually is positive with extensive skin hemorrhages below the constricting band The test however is positive in other conditions and so the result is not diagnostic of purpura This usually is called the Rumpel Leede's[69] test or tourniquet test Somewhat similar as to significance is the trauma test in which local hemorrhage follows the blow of a percussion hammer or similar object against the skin over a bony surface such as the sternum or tibia Koch's[9] phenomenon is the appearance of subcutaneous hemorrhages following a number of needle pricks close together Localized suction to the skin also will cause petechiae Dalldorf test in susceptible persons The subcutaneous injection of 1 to cc of a 0 2 per cent sodium chloride solution will be followed by a subcutaneous hematoma (Hess[71] puncture test as modified by Leschke) as a rule in thrombocytopenic purpura The gravitational factor in thrombocytopenic purpura i e the tendency for petechiae to preponderate in dependent parts of the body is another evidence of the capillary factor in the mechanism of the purpura

Direct microscopic observation of skin capillaries in the finger now is possible (capillaroscopy) by a method originated by Lombard and perfected by many workers. Elmer[3] has studied in this way a patient with thrombocytopenic purpura and found, as in hemophilia, dilated capillaries with delayed contraction following a razor blade cut. After such trauma a larger drop of blood arose from a single injured capillary *than in normal controls, more than he observed in any other conditions* than hemophilia and thrombocytopenia. Elmer believed that both the delayed contractility of the capillary and the defective clotting of the blood in the tissues played a role in the increased bleeding following capillary injury in these two conditions. On the other hand v. Bermuth[4] in one case of essential and one of symptomatic thrombocytopenic purpura found that the capillaries reacted normally to a cut.

Possibly platelets are normally concerned with the preservation of capillary integrity in addition to their part in clotting to stop hemorrhage from valuable capillaries. Capillary integrity in some patients may return to normal even though thrombocytopenia persists, sometimes splenectomy ends the purpura, and yet platelets only temporarily rise to normal number. Usually however these two phenomena coincide. Certain observations[1, 13, 17, 218] have suggested that an anticoagulant, indistinguishable from heparin, was present in patients with thrombocytopenia and a possible factor in the mechanism of their purpura. Two substances, protamine sulfate and toluidine blue, are capable of binding heparin and rendering it biologically inactive, so far as its anticoagulant properties are concerned, without affecting any other phase of the clotting mechanism. These substances have been found effective in inhibiting bleeding in the presence of marked thrombocytopenia without altering the platelet count. Experiments on dogs with an irradiation (roentgen ray) hemorrhagic condition have shown this, these irradiated *animals have marked thrombocytopenia* and *prolonged bleeding* and clotting time. Allen and associates[13] also have given these substances intravenously to patients with thrombocytopenic purpura (4 cases of secondary type with leucemia and 2 cases of the idiopathic type) and found that generalized oozing of blood was stopped except from ulcerated areas. This work has thrown additional light on the problem of the mechanism of thrombocytopenic purpura and may introduce into their treatment an additional means of control of the purpura. Holonbek and associates[1] also have used toluidine blue with good results in stopping bleeding.

Frank[4] suggested capillary stasis and the theory of micro-traumata as the immediate cause of the bleeding Testing with a tourniquet about the arm often does show by the appearance of small hemorrhages in the arm below the tourniquet that capillary walls are vulnerable Bedson[67] in experimental studies demonstrated that altered vascular reactivity as well as thrombopenia plays a role Further indication of a vascular role is indicated by the observations of Macfarlane[68] that normal capillaries contract after injury but that when bleeding time is prolonged contraction is greatly decreased

Blood in Thrombocytopenic Purpura

Reduction in Number of Blood Platelets

In 1881 Brohm and Krauss[5] and in 1887 Denys[6] independently described cases of purpura with platelet deficiency as shown in blood smears In 1890 Hayem[7] actually counted the platelets in a patient with hemorrhagic purpura Since then there has been a steadily increasing number of observations of platelets in relation to purpura of various sorts Pratt[3, 78] Duke[8] and Minot[80] in this country have contributed numerous observations of platelet counts in individual cases As different methods of counting platelets are used and as they give somewhat different figures for normal individuals this must be taken into account when considering platelet counts Pratt's[3, 81] sodium metaphosphate method is one of the best and gives an average normal count of 469 000 platelets per cubic millimeter of blood Hayem's method gives 50 000 as normal Dameshek's[3] method with isotonic aqueous solution of sodium citrate containing brilliant cresyl blue gives counts from 400 000 to 900 000 A good plan to follow is to check counts on patients against a count on a normal person as control

In thrombocytopenic purpura counts have been reported below 1 000 but it is very probable that these were incorrect owing to the method used Counts of 8 000 or less depending on the method used have been observed by Duke[79] (6 000 or below 1 000) Minot[8] Pratt[2, 81] (7 000) Selling[5] (500) Bull and Rosenthal[9] (4 000) Corr[83] (500 and 3 600) Naegeli[84] (6,400) Herfarth[86] (8 000) and others during the stage of bleeding Recent reports tend to record somewhat higher platelet counts when at their low level possibly from improvements in counting technic As examples Doan and Wright[5] give a patient with 16 000 as

low count, Dameshek and Miller[1] 45,000, 25,000, 20,000 and 15,000 and Valentine 37,000, 17 500 and 11 000. Various levels of platelet count have been set below which bleeding takes place, Minot[80], 60 000 Brill and Rosenthal[8], 10,000, Duke[9], 40,000 to 75,000, these variations probably depend both on the type of purpura case (acute or chronic) and on the method employed in counting the platelets. With improvement and cessation of bleeding the platelet count rises above these limits although it is a striking fact that splenectomy may result in cure with only a temporary rise in platelets above the level at which bleeding previously took place.

Morphological Changes in the Blood

The platelets themselves show no characteristic changes in thrombocytopenic purpura. Sometimes they are larger than the average normal and they may show considerable variation in staining reaction. In typical cases of thrombocytopenic purpura the other blood elements, as already explained following the hemorrhages show the changes ordinarily found in post hemorrhagic anemia. There is a moderate to marked fall in the red count depending on the blood loss, the cells show achromia and the color index tends to be low, there is a slight variation in size and shape, some polychromatophilia and stippling occur, occasional normoblasts are seen, reticulated red cells appear in increased number when appropriate staining methods, as brilliant cresyl blue, are used and these constitute one of the best evidences of bone marrow activity so far as red cell formation is concerned. White cells are moderately increased there being a moderate polynuclear leucocytosis both relative and absolute, at times there is a slight relative lymphocytosis. These several changes in red and white cells vary in individual cases depending both on the stimulus to hyperplasia and the ability of the marrow to respond, response is less in those cases where toxic substances injure the bone marrow with respect to red and white cell forming elements and on account of this we have a group of atypical cases.

Prolonged Capillary Bleeding Time

Capillary bleeding time is prolonged. Duke noted that in thrombocytopenic purpura bleeding from a small skin lesion was prolonged. Duke's method was to make a small incision in the ear lobe and at

intervals of thirty seconds to blot up on absorbent paper the blood that had flowed In normals such a hemorrhage stops in one to three minutes Prolongation beyond ten minutes is distinctly abnormal In thrombocytopenic purpura the bleeding time may be from twenty minutes to several hours The bleeding time serves as an index of the hemmorhagic tendency when it is prolonged platelet counts are low According to Minot a normal bleeding time occurs in purpura hemorrhagica only when the platelet count is above 60 000 per cubic millimeter, others set differing levels of platelet counts for this In similar fashion bleeding time from vein puncture may be prolonged in this condition but often this is not the case even though ear puncture gives a prolonged bleeding time

Operative Bleeding Time

In thrombocytopenic purpura as a rule there is no increased tendency to bleeding at operation although at times this may not be the case In other words although capillary bleeding time is prolonged there often is no increased tendency to hemorrhage from larger vessels Splenectomy can be safely recommended as a therapeutic procedure without fear of uncontrollable hemorrhage during or following operation

Non retractility of Clot

Failure of retraction of the blood clot as pointed out by Hayem is another feature of the blood in thrombocytopenic purpura Normal blood when allowed to stand forms a firm retracted clot and squeezes out a clear serum In thrombocytopenic purpura the clot is soft jelly like and fails to squeeze out the serum in a normal way This phenomenon is associated with the low platelet count and varies with variations in the platelet count

Coagulation Time

Coagulation time varies but usually it is within normal limits The various factors concerned in coagulation fibrinogen thrombin antithrombin and prothrombin vary within normal limits in most of the cases

Essential, Primary or Idiopathic Thrombocytopenic Purpura

Definition and Terminology

This is the form of purpura in which the most important causative factor is thrombocytopenia with, however, vascular vulnerability contributory to its mechanism as already has been discussed. It is characterized by recurring bleeding into the skin or mucous membranes. This form of purpura has been termed essential, primary or idiopathic indicating that there appears to be no demonstrable cause other than a disturbance brought about in some way in the process of formation and function of platelets in relation to the prevention of the escape of red blood cells from small blood vessels. In this mechanism the spleen has a definite role (hypersplenism).

Etiology, Pathological Physiology and Pathology

These features have been discussed already under the heading Thrombocytopenic Purpura and need not be repeated at this point.

Clinical Features

Cases of essential, primary or idiopathic thrombocytopenic purpura may be divided into acute and chronic. The chronic cases can be subdivided further into two groups, chronic intermittent and chronic continuous. Chronic forms have been reported as being much more common than acute, in Whipple's[4] collection of cases 8 were acute and 73 chronic. Recent reports, however, indicate that acute cases or cases symptomless except during acute exacerbations preponderate. The duration of an attack is from a few weeks to several months in the acute and intermittent forms. The interval between attacks in the latter may be anywhere from a few months to many years. Bensaude and Rivet[5] report an interval of 7 years between the second and third attack, Forster[58] cites a case with an interval between attacks of 30 years. The disease may persist for years, Pratt[3] cites a case, beginning at the age of 10, who had frequently recurring epistaxis with occasional crops of purpura over a period of 36 years.

In some of the cases there are definite hereditary and familial elements. Leschke and Wittkower report a woman (case 11 in their

paper) with thrombocytopenic purpura whose daughter at birth showed purpuric spots with new spots a few days later and blood in stools and urine for 9 days and whose blood on the sixth and ninth days after birth showed normal coagulation time delayed bleeding time and decreased retraction of clot At birth a blood smear made from the navel showed an almost complete absence of platelets Liebling also has reported purpura in mother and child and Morrison and Samwick[90] in maternal grandmother mother and child Leschke and Wittkower report a woman (case 12) with moderate platelet deficiency (80 000) and severe hemorrhage following abortion who had a brother who from childhood had frequent severe nose bleeds and whose daughter (one of four children) for two years had had almost daily nose bleeds and was found to have a platelet count of 126 000 Hess[1] has reported several instances of hereditary thrombocytopenic purpura Other reports have been made by Bailey and McAlpin[9] Schefrin and Schechtman[93] and Davis[94] and Barclay[95] Cases of purpura with an hereditary element may be confused with hemophilia although the features of the blood characteristic of each should distinguish them There is the further difference that hereditary purpura is not confined to the male as is hemophilia In some families both conditions appear and instances of a male bleeder of the hemophiliac type and a female bleeder of the purpuric type have been observed Hess[91] reports two such families Atypical blood findings may occur in this group as reported by Minot[9] and by Buckman[96] In Minot s patients there was a prolonged bleeding time without decreased platelets and with normal coagulation time while Buckman s patients showed both prolonged bleeding and coagulation time with normal or slightly increased platelets Such cases further complicate the situation and render classification difficult Hess[91] even has seen a case (a girl of 4) which he regards as both hemophiliac and purpuric because there coexisted delayed coagulation time and platelet deficiency Such atypical blood findings also confuse classification very greatly

Some observers adhere to very strict criteria for inclusion of these hereditary and familial cases as cases of true essential primary or idiopathic thrombocytopenic purpura and exclude many that in the past have been included For example Morrison and Samwick require for inclusion the following criteria (1) purpura with petechiae and ecchymoses (2) increase in bleeding time (3) increase in clot retraction time (4) decrease in platelets (5) no change in coagulation time (6) no change in prothrombin time (7) either normal or increased number of megacaryocytes and/or immature megacaryocytes (8) normal vitamin

C content, (9) positive tourniquet test, (10) normal or slightly enlarged spleen, (11) absence of adenopathy, (12) leucemoid reaction with leucocytosis and polynucleosis, especially in presence of active bleeding (13) absence of lymphocytosis especially in presence of active bleeding and (14) absence of leukopenia Applying these criteria, they exclude all but one of 14 cases reported in the literature the case of Waltner[37], and add one case of their own Many of these cases seem to fall in the non-cytopenic rather than in the cytopenic group The non cytopenic group will be discussed farther along under the subheading Familial and Hereditary Purpura

Essential thrombocytopenic purpura may occur at any age from birth on, but the disease is definitely most frequent in youth before puberty As to sex, females seem to preponderate but not in all reported series of cases

Clinically this group of patients is characterized by hemorrhages into the skin and from the mucous membranes Sometimes skin hemorrhages occur without bleeding from mucous membranes and vice versa In intermittent types now the one or the other may occur, or both may appear at the same time There are cases in which hemorrhage is confined always to one place, skin or mucous membranes the latter being infrequent The amount and persistence of the hemorrhages vary much from patient to patient

The skin lesion may consist of irregularly scattered or very diffusely distributed small ecchymoses, or they may be of very great size with all gradations between The individual lesions as time goes on show the progressive changes in color of an ordinary subcutaneous hemorrhage Usually the lesions are not elevated but this is not always true although rarely are they exudative in types as is frequent in the anaphylactoid group of cases of purpura At times gravity has some influence on the appearance of skin lesions Lesions may reappear on a patient's legs when he gets out of bed Curiously enough, although tests show capillary vulnerability, skin lesions rarely seem determined in position by factors irritating or slightly traumatizing the skin It is stated that reabsorption of large hemorrhages is unaccompanied by bilirubinemia

Purpuric spots may develop gradually or with great rapidity There seems to be no special predilection for certain parts of the body and no definite tendency to symmetrical distribution

Of bleeding from the mucous membranes, epistaxis occurs most frequently Bleeding from the gums or other parts of the mouth probably comes next in order of frequency Bleeding may take place from

any mucous membrane gastrointestinal tract trachea larynx bronchi uterus and vagina kidney and bladder Hematuria in thrombocytopenic purpura is not the result of nephritis as it often is in the anaphylactoid forms of purpura[103] Bleeding from the lungs occurs but is rare Hemoptysis may be an initial symptom[99] Purpura may be localized to the stomach[104] Purpuric spots may appear on serous membranes but hemorrhages into serous cavities are rare Hemorrhages into the tissue of a viscus are surprisingly infrequent but do occur Hemorrhage into the adrenals among others have been reported Cerebral hemorrhage with resultant hemiplegia aphonia or other disturbance is not uncommon Several cases of hematomyelia as a result of thrombocytopenic purpura have been described[100] Hemorrhage into the eye may take place with dimness of vision or total blindness [95] Bilateral optic atrophy has been reported as a sequence[101] Hemorrhage into external rectus muscle of eye has been reported causing strabismus The ophthalmoscope may show retinal hemorrhages of varying extent either into vitreous or retina Hemorrhage into joints which *is* frequent in hemophilia is rare in thrombocytopenic purpura Some deny its occurrence but apparently it does occur with resultant symptoms of arthritis According to Pratt[2] rheumatic pains in the joints in not very uncommon Chronic leg ulcers may occur[102]

Failure to make the diagnosis occurs at times in the presence of hemorrhage from some viscus as the stomach rectum or uterus because of not thinking of thrombocytopenic purpura as the possible cause and consequently not examining the blood to see if there is a thrombocytopenia Uterine bleeding (menorrhagia[103]) for example may be attributed to some local cause with resultant surgical treatment curettage or even hysterectomy instead of recognizing its thrombocytopenic cause and consequent correct treatment It is wise to *think* of the possibility of thrombocytopenic purpura in such patients and before advising any therapy to make sure of the diagnosis by studying a blood smear and making a tourniquet test

Occasionally the spleen shows marked enlargement usually it is not enlarged in essential thrombocytopenic purpura Possibly the cases with marked enlargement of the spleen with enlargement of the liver are some form of secondary thrombocytopenic purpura as a case observed at the Peter Bent Brigham Hospital which turned out to be a case of aleucemic leucemia with secondary thrombocytopenic purpura although until a very few days before death the blood picture gave no

suggestion of leucemia The efficacy of splenectomy seems to have no relation to the size of the spleen

Visceral manifestations are very infrequent in this type of purpura apart from those resulting directly from hemorrhage Fever occurs in acutely ill patients, in those with marked degree of secondary anemia or as the result of complicating infection of some sort

Secondary anemia after severe hemorrhage may be a marked feature the patients showing pallor and the circulatory disturbances common to anemia of any sort

In some cases a precipitating factor may be found Menorrhagia often is one as are infections, such as pneumonia measles scarlet fever, chicken pox vaccinia and small pox Menstruation frequently becomes a genuine danger to the patient with thrombocytopenic purpura

Diagnosis

Thrombocytopenic purpura is recognized by finding the blood changes as already described Difficulty arises only in those patients with atypical blood findings Essential is separated from symptomatic thrombocytopenic purpura by the failure to find evidence of any condition to which the purpura might be secondary

Scurvy may be confused with this form of purpura, but the general clinical features of scurvy such as spongy gums hemorrhagic infiltration of the muscles especially in the lower leg, and subperiosteal hemorrhages should distinguish them If not, the lack of platelet deficiency in scurvy should be enough to separate them The possible confusion with hemophilia already has been referred to The diagnosis from other types of purpura will be discussed under those headings

Prognosis

Prognosis has been changed very markedly with the improvement in the surgical handling of patients with essential thrombocytopenic purpura, especially of the very ill acute cases so many of whom formerly died without or with splenectomy Splenectomy at present with the use of repeated transfusions of blood has a low mortality and very often is curative With its use prognosis now is good for patients with essential thrombocytopenic purpura even for acutely ill cases unless

its use has been delayed too long Many of the more mildly sick patients recover spontaneously recovery often facilitated by blood transfusions some of the sicker ones do too

Schwartz[20] in a study of the bone marrow of 30 cases of thrombocytopenic purpura counted eosinophiles in relation to neutrophiles Later with Kaplan[17] he studied similarly 70 more patients In 100 patients with increased eosinophiles i e over 50 per 1 000 neutrophiles 37 recovered spontaneously, 25 had successful results from splenectomy none died In 18 patients with fewer eosinophiles in the bone marrow splenectomy was successful in 8 and 8 died after splenectomy were unimproved 8 of 35 with low eosinophile counts recovered spontaneously Schwartz regards bone marrow eosinophilia the eosinophilic index as he calls it as indicative of an allergic mechanism and believes its presence is a good prognostic omen with a high eosinophilic index there is a marked tendency for spontaneous recovery and practically certain cure by splenectomy with insignificant operative mortality

Treatment

Discussion of treatment of essential thrombocytopenic purpura can be reduced to very simple terms transfusions of blood and splenectomy Numerous other methods of treatment suggested in the past can be dismissed now with the statement that claimed good results have failed of continued materialization Parathormone is one of these recently retried[2 9]

Transfusions of Blood — As the chief causative mechanism is deficiency of platelets in the circulating blood the obvious thing to do is to replace them as promptly and as thoroughly as is possible Since platelets have but a brief life cycle blood as fresh as is available should be used for transfusions taking all the usual careful precautions to insure matching of the donor s blood with that of the recipient Since many platelets are needed large transfusions should be given slowly so as not to overburden the recipient s circulation Fortunately the patient having lost blood by hemorrhage there is need for both blood bulk with its red cells and for the contained platelets and so relatively little danger of overburdening the circulation As platelets normally disappear from the blood in a few days repetition of transfusions even after blood bulk has been restored to the patient is needed Daily transfusions may be required for some time as indicated by continuing bleeding phenomena

and reduced platelet counts Many patients following such transfusions stop bleeding some permanently, more for varying periods of time until return of purpuric symptoms occur

Splenectomy — Patients with recurring purpura and very ill patients following preliminary transfusions of blood, should undergo splenectomy, since a large proportion of patients with essential thrombocytopenic purpura are cured by splenectomy, unless accessory splenic tissue has been left behind If recurrence of purpura occurs after splenectomy this should be considered as a probable cause, and if remaining splenic tissue seems probable, another operation should be undertaken for its removal If preliminary blood transfusion is carried out thoroughly with properly matched blood and a competent surgeon is available to perform the operation, mortality from splenectomy now is low Even in the very acutely ill patients with preliminary transfusions splenectomy is the treatment of choice

In considering the desirability of splenectomy it is to be remembered that in thrombocytopenic purpura apart from the danger of death purpuric hemorrhages may be causative of focal injury of tissues recovery from which even if bleeding stops will not take place Splenectomy constitutes a prophylactic procedure under these circumstances

In many patients splenectomy is dramatic in its effects, bleeding stops almost immediately and platelets rapidly reappear in the circulating blood In many patients after splenectomy platelets remain at levels above the critical point of hemorrhage In some patients however platelets may fall again to abnormally low levels, interestingly some of these patients may not relapse into a purpuric state Those that do relapse may have accessory splenic tissue which was not removed at operation These patients that do not relapse, although platelets return to low levels indicate that platelet deficiency is not solely the cause of thrombocytopenic purpura In a few patients splenectomy does not restore platelet counts to normal, in some of these purpura ceases while in others it persists

As already mentioned under Prognosis bone marrow eosinophilia may be an indication that occurrence of spontaneous recovery is probable Probably eosinophilia of less degree may indicate a more probable recovery after splenectomy, little data of this nature however is as yet available

The changes following splenectomy and the role of the spleen in the causation of thrombocytopenic purpura already has been discussed under the heading Pathological Physiology and Pathology

Toluidine blue also may be of therapeutic value in these patients as discussed later on in the section Hyperheparinemia

Hereditary Thrombocytopenic Purpura

Rarely thrombocytopenic purpura may be hereditary Epstein Lozner Corbey and Davidson[311] have collected from the literature 37 such cases and added 7 of their own Unlike most other varieties of thrombocytopenic purpura this hereditary form is sharply self limited present at birth of 17 cases surviving after birth or sufficiently studied duration was 30 days or less in 16 30 to 60 days in 5 60 to 90 in 3 90 to 120 in and beyond 120 in 1 there were no relapses Being a self *limited disease in the child the only treatment needed is supportive* treatment through the acute episode and if anemia becomes marked from blood loss a blood transfusion followed by iron given orally

Whether or not a therapeutic splenectomy had been performed on the mother prior to pregnancy had no influence on the occurrence of this hereditary thrombocytopenic purpura in infants Hereditary thrombocytopenic purpura is not however a constant sequence to this disease in the mother since the presence of thrombocytopenic purpura in mothers has been reported during pregnancy without its appearance in the child In the 46 pregnancies with thrombocytopenic purpura collected by Epstein and associates[311] maternal mortality was 8 7 per cent while 61 per cent of the children were born dead or died within 3 days post partum with only one third of them having definite evidence of thrombocytopenic purpura while of the 73 9 per cent born living approximately one half had purpuric manifestations

These cases fit in general into the theory of Frank[4] that the thrombocytopenia of this form of purpura results from inhibition of bone marrow megacaryocyte activity by an agent produced in the spleen since in study of the bone marrow of some of these mothers hyperplasia of the bone marrow was found at the same time that there was decreased formation of platelets This substance possibly of hormonal nature would seem to have been transferred across the placenta into the fetal circulation However such a substance must be independent of any activity of the spleen since splenectomy in the mother failed to prevent thrombocytopenia from developing in the fetus and infant whether surviving or not and in this respect does not conform to the theory of Frank

Cyclic Thrombocytopenic Purpura

There is a very rare form of cyclic thrombocytopenic purpura probably in the primary or essential rather than in the secondary or symptomatic group although there is the suggestion that it results from an endocrine disturbance Demmer[106] has reported a case in a 60 year old man who had been impotent for 18 years and who for 6 years had had recurring purpura at intervals of 28 days His blood showed severe thrombocytopenia preceding and accompanying the purpura, sometimes with relative neutropenia and compensatory lymphocytosis Cyclic neutropenia without purpura is of a little more frequent occurrence as reported by Reimann[107] Doan[108] Reznikoff[109] Leale[110], Rutledge and associates[111] and Thompson[11] the last three having studied the same case in infancy again when 19 and about 4 years later, the cyclic neutropenia patients had some one or several of various accompanying symptoms, such as malaise headache body aches sore throat, oral ulcers, canker sores and abdominal pain

Thrombocytopenic Purpura with Generalized Platelet Vasothromboses

This is a special form of thrombocytopenic purpura constituting a distinctive clinical syndrome and having a mechanism apparently differing from the mechanisms of the more usual forms of thrombocytopenic purpura whether essential (primary) or symptomatic (secondary) The terms, thrombotic thrombocytopenic purpura[318], febrile thrombopenic purpura[31] and thrombopathic thrombocytopenia[319], also have been used for it The salient clinical features are fever, thrombocytopenia, a rapidly progressing hemolytic type of anemia quite often (in 3 of 5 recently reported cases[9]) purpura and bizarre non localizing cerebral and visceral manifestations, icterus of mild degree occurred in 12 of 21 reported cases, these features are characteristic enough to make possible a correct diagnosis of the condition

The mechanism of the thrombocytopenia apparently is a disappearance from the circulation of the great majority of the platelets because they have aggregated in very great numbers to form platelet thrombi in small blood vessels arterioles capillaries and venules usually commencing at the arteriolar capillary junction Usually there is increased bleeding time defective clot retraction with normal coagulation time and increased capillary fragility Of the 21 reported cases[9] males as well

as females both white and colored have been affected in age they have ranged from 9 to 66 The course of the disease has varied from 1 to 3 weeks with an occasional patient living for a few months A fatal outcome has been universal in reported cases Purpura may developed only late in the disease or not at all It is the patient with purpura that interests us in this discussion

The pathological lesion[59] develops from a focal vascular lesion of capillaries and arterioles seemingly non inflammatory consisting of a *segmental accumulation of hyaline material beneath the endothelium of* a capillary and between the endothelium and musculature of an arteriole which with rupture of the endothelium provides a focus for accumulation of platelets to form thrombi Subsequently reactive endothelial proliferation occurs about enlarging thrombi with still later organization and fibrosis The process seems to be an intermittent one with the *thrombi developing in showers and crops* and hence the variations in the appearance of the thrombi in a given case from early ones generally hard to find showing the hyaline change to later ones with platelet thrombi and proliferated endothelium and still later ones with fibrin and final ones with organization and fibrosis The thrombocytopenia is believed to be due to removal from the circulation of the very large numbers of platelets *needed in the formation of the myriad thrombi*

This group of cases probably occurs more often than indicated by the relatively few reported cases[60 to 66] The symptoms result chiefly from the obstructive effect of thrombi in small blood vessels which hinder nutrition to focal areas These disturbances are likely to be most in evidence in the central nervous system where there is so close a *relationship between circulation and cell function* In these patients such nervous manifestations as aphasia dysphagia decreased strength and/or increased spasticity in arms and legs hypo and/or hyper active reflexes occur these may wax and wane in intensity or disappear and then return Rarely psychotic symptoms occur these may be the early *manifestations of the disease*[61] *The vascular lesions may cause cardiac* disturbances such as tachycardia gallop rhythm enlargement dyspnea and electrocardiographic abnormalities if the focal obstruction to the circulation results in focal myocarditic lesions Thrombi in the glomeruli usually cause albuminuria with slight to moderate hematuria However symptoms referable to vascular lesions in body *tissues other than the brain usually are not much in evidence*

Transfusion of blood platelets is reported as a successful treatment[119]

Secondary or Symptomatic Thrombocytopenic Purpura

Definition — Secondary or symptomatic thrombocytopenic purpura differs from essential, primary or idiopathic thrombocytopenic purpura as already defined, only in that each case of the former has an assigned probable cause

Etiology, Pathological Physiology and Pathology

As purpura has been studied more and more intensively, an ever increasing number of causative factors have been reported for secondary or sympotomatic thrombocytopenic purpura The majority of these factors can cause either thrombocytopenic or non thrombocytopenic purpura As seen in the classification of purpura given on an earlier page causative factors of secondary or symptomatic thrombocytopenic purpura can be grouped under various headings as (1) blood diseases (2) other diseases with certain disturbances in the blood and/or the bone marrow (3) certain types of disease of the spleen and of the liver (4) infections and infectious diseases (5) intoxications including drug idiosyncrasies, (6) allergy, (7) avitaminosis, (8) radiation

Blood diseases with bone marrow lesions in certain stages cause thrombocytopenia because the lesion causes degenerative changes in the megacaryocytes or marked decrease in their number in this way decreasing the formation maturation and extrusion of platelets into the circulation until the number of platelets falls to levels at which purpura appears Leucemia with great numbers of leucemia cells in the bone marrow crowding on the megacaryocytes is an example of one way in which a blood disease can cause thrombocytopenia In some cases of pernicious anemia the process involves not only the maturation of red blood cells but also of platelets and white cells so that there results not only erythrocytopenia but also thrombocytopenia and leucopenia in varying degrees with some patients developing sufficient thrombocytopenia to have purpura Aplastic anemia is another blood disease in which with its causative bone marrow aplasia all cells including megacaryocytes decrease in number to cause deficiencies in the circulation of the cells which they form including blood platelets Some patients with agranulocytosis, as a result of the lesion in the bone marrow involving also megacaryocytes and platelet formation develop thrombocytopenia in addition to the agranulocytosis Bone marrow sclerosis of any

cause also may reduce megakaryocytes and lead to thrombocytopenic purpura

In blood diseases as enumerated in the preceding paragraph the occurrence of thrombocytopenic purpura is not a constant feature usually it occurs late in the disease and especially in the severely ill patients in whom the disease is running a rapid course In these patients purpura usually but not always is of the thrombocytopenic type

Similar in mechanism to the thrombocytopenic purpura of blood diseases is the occurrence of purpura in patients with widely spread carcinomatosis of the bone marrow or with other forms of widely spread metastatic neoplasm of the bone marrow It may occur also in certain widely spread primary bone marrow diseases such as multiple myeloma and lymphocytoma Any bone disease such as marble bone disease causing widely spread fibrosis of or encroachment on the bone marrow similarly may lead to thrombocytopenic purpura

Another possible mechanism of purpura in patients with multiple myeloma has been suggested by Lerner and Watson[113] namely that abnormal globulins cryoglobulins by their concentration in the blood and their unusual solubility properties have increased blood viscosity and lead to purpura thrombosis possible precipitation of this globulin in capillaries and oozing of blood from mucous membranes the terms purpura cryoglobulinemia or better purpura hyperglobulinemia have been suggested for them as the globulin is not in all cases cold precipitable i e is not a cryoglobulin Barr and associates [9] have studied two such patients who showed as the only change in clotting mechanism a very slow clot retraction 13 hours for completion

Agress and Smith[1] [4] have reported the case of a 55 year old man with purpura hemorrhagica apparently resulting from the accumulation in many cells of the body including the histiocytes of the bone marrow and monocytes of the blood of needle like or rod shaped crystals which they considered as probably a form of protein and believed that these caused the purpura with anemia and decreased number of platelets If this assumption is correct then here is a different mechanism of thrombocytopenic purpura than the usual ones

Infectious mononucleosis is another disease with blood changes in which thrombocytopenic purpura may occur[124]

In all of these the pathological physiology is in the main a mechanism of injury to the megakaryocytes inhibiting or stopping the formation of platelets by them Bone marrow studies show degenerative changes in megakaryocytes or decrease in their number platelets are

decreased in number, and some of them may be abnormal in appearance

In certain diseases, in which the spleen is enlarged and shows the tissue characteristic of the disease or merely is hyperplastic thrombocytopenia and purpura may develop Among these are Hodgkin's disease sarcoid Gaucher's disease, tuberculosis of spleen Felty's syndrome[300] splenic vein thrombosis Banti's disease and certain varieties *of cirrhosis of the liver In some of these besides the thrombocytopenia* there is anemia and leucopenia in other words panhematopenia In such patients splenectomy often results in increase in platelets and disappearance of the purpura or the purpura may remain absent even though platelets return to or remain at a low level .Obviously splenectomy will not influence the course of the fundamental disease in these patients

In this type of purpura Dameshek and Miller[1] have found in the bone marrow of these patients studied by them (1) an increase in megacaryocytes in about the same proportion as in acute essential thrombocytopenic purpura (2) a normal proportion of platelet producing cells (3) no increase in megacaryoblasts or decrease in promegacaryocytes (4) normal production of platelets from adult megacaryocytes and (5) no increase in degenerated forms They thought that the thrombocytopenia in these cases was a form of simple hypersplenism but fail to state how the thrombocytopenia was produced by the spleens of these patients Doan and his associates consider that patients of this group develop their thrombocytopenia as the result of very active intrasplenic phagocytosis of platelets a condition which Dameshek doubts stating as a footnote in one of Doan's papers these observations are at variance with our own which indicate an unusual inhibitory effect of an overactive spleen upon the bone-marrow rather than one wholly due to unusual sequestration and phagocytosis within the spleen Both agree however to the important role played by the spleen and the good results on the lowered platelet count from splenectomy Further observations are needed to decide whether there are two mechanisms effective in this group of patients or if only one is effective which one that suggested by the studies by Dameshek and his group or that suggested by the observations of Doan and his group

As with the spleen under certain conditions the liver has an influence on platelets and on capillary fragility besides being a factor in the mechanism of hypoprothrombinemia The latter is discussed later on in this chapter in the section on Hypoprothrombinemia It is parenchymatous disease of the liver which in particular is causative of thrombocytopenia and increased capillary fragility [6], these may occur sepa

rately or in combination and may cause bleeding of purpuric character. Hepatitis, acute or chronic, and cirrhosis of the liver cause these changes even without the presence of jaundice more frequently than do obstructive jaundice from such causes as obstruction of the common bile duct by calculus, stricture or cancer of the ampulla of Vater or the head of the pancreas. Hepatitis has had of late increasing importance by reason of the frequency of occurrence of homologous serum and viral types of hepatitis. Investigation of these patients[6] has shown in varying degree an increase in the number of petechiae resulting from a standardized Rumpel-Leede test as evidence of increased capillary fragility, a decrease in the number of circulating thrombocytes, hypoprothrombinemia and evidence of an increase in a circulating anticoagulant, possibly heparin.

These patients often show an increased tendency to bleed from the gums and/or a history of recurrent epistaxis or melena with a not infrequent continued oozing from cuts, punctures or abrasions of the skin and easy bruising from trauma. These patients often show hypoproteinemia or hyperglobulinemia or both. There is no necessary parallelism between these several abnormalities just mentioned, nor is there any definite parallelism between them and the tendency to bleed.

The clinical picture and the various clinico-pathological changes are in essential those found in primary or essential thrombocytopenic purpura. It is important to distinguish them, as can be done by tests of liver function which by their decrease will point to the liver disease as causative of the purpuric manifestations, if for no other reason, to prevent advising splenectomy as a therapeutic measure. In some patients to make certain of liver disease a punch biopsy of the liver with histological study of the specimen should be carried out, particularly in those patients in whom the liver is enlarged but there is no or minimal jaundice.

In the course of various infections and infectious diseases purpura may develop. Sometimes it is a thrombocytopenic, sometimes a nonthrombocytopenic purpura. In the former group cases have been reported with various forms of infections and infectious diseases as follows: septicemia, meningococcus and gonococcus infection, subacute bacterial endocarditis, typhoid, typhus, Rocky Mountain spotted fever, scarlet fever, measles, German measles (rubella), smallpox, vaccinia, chicken pox, plague, yellow fever, undulant fever, pneumonia, infectious mononucleosis, acute hepatitis (catarrhal jaundice, Weil's disease), onyalai, influenza, malaria and rheumatic fever. In some of these

patients there is always the possibility that medicinal therapy, and not the disease itself has caused the purpura, inasmuch as some of the drugs being used are considered to cause, at times, thrombocytopenic purpura However in many of these patients there has seemed no probable drug cause

In many of the conditions, just cited thrombocytopenic purpura is a rare manifestation, and so opportunity to study them by modern technics including study of repeated bone marrow smears has been very restricted or entirely lacking Consequently their pathology and pathological physiology is little known Probably the platelet deficiency in these cases results in disturbance somewhere in the megacaryocyte to platelet production mechanism much as happens in the next group

The group of symptomatic or secondary thrombocytopenic purpura due to intoxications is of much clinical interest because of the very serious consequences from its development, these patients not infrequently becoming very ill or, even in spite of all efforts at treatment of them dying In some industries such purpura is a serious risk even if its development is not frequent The same applies all the more to its development as a drug idiosyncrasy inasmuch as many of the drugs play an important role in therapeutics Fortunately for many of them it is an infrequent happening which in itself suggests that the patient has developed a susceptibility, probably of an allergic type rather than that the drug has an inherent toxicity on the mechanism of platelet production fortunately many many patients take these drugs without developing purpura or other similar toxic manifestations In some patients this susceptibility can be demonstrated by test reactions as in other forms of allergy

Among chemicals in use in industries thrombocytopenic purpura has been reported as caused by aniline arsenic, benzene, benzol colloidal silver, trinitrotoluol

Among drugs reported to have caused secondary or symptomatic *thrombocytopenic purpura there are the arsenicals (arsphenamine neo* arsphenamine[116] bismarsen mapharsen[114 115]), the sulfonamides (sulfanilamide sulfadiazine sulfamerazine sulfapyridine sulfathiazole) phenobarbital sedormid gold salts[30] quinine quinidine [3 31 317] euchinine iodides, sodium salicylate[117] chenopodium dinitrophenol tridione[118 119 120] mesantoin [67 306], propylthiouracil [98 307], penicillin[308] and presidon[316] This list probably will increase as more patients are observed after taking some of the newly introduced drugs In some of these as sedormid frequency of purpura is great enough to make it almost imperative to

use another drug with similar therapeutic action but with far less or no probability of causing purpura

In all of these toxic varieties of thrombocytopenic purpura the mechanism of thrombocytopenia theoretically could be at any level of platelet formation from the megacaryocyte to the extrusion of the platelet into the circulating blood or be due to an injury or destruction of the platelets in the bone marrow or after they reach the circulating blood The megacaryocytes might show evidences of injury or destruction normal looking megacaryocytes might cease to form platelets formed platelets might show signs of degeneration in either bone marrow or blood or platelets might undergo lysis after their formation any one of these changes theoretically is possible In some patients it is possible that not only *platelet formation* but also red cell and leucocyte formation may be affected with as a result thrombocytopenia leucopenia and thrombocytopenia or as it is called panhematopenia These patients would show anemia and leucopenia as well as a low platelet count and probable purpura Just what is the pathological physiology in individual cases is not certain Only a few patients in this group seem to have had careful examination of peripheral blood and bone marrow by modern methods Even with the same causative drugs different findings have been reported possibly dependent on the time in the development of the purpura at which the examinations were made since very rapid return to normal may occur in both bone marrow and peripheral blood As an example of this in a case caused by mepharsen Schwartz and Van der Heide[114] report a lack of bone marrow change while Schrumpf[31] in another mepharsen case described in the bone marrow an increased number of megacaryocytes chiefly young forms In a patient with acute thrombocytopenic purpura caused by neoarsphenamine Hattersley[118] found in the bone marrow on the second day of the disease complete absence of megacaryocytes and of platelets with a marked increase in megacaryoblasts many of them showing signs of degeneration and on the eighth day the reappearance in considerable numbers of megacaryocytes some of the immature type but none with signs of degeneration many actively producing platelets Hattersley s patient received BAL in treatment In a patient with rheumatoid arthritis treated with large doses of sodium salicylate Rappaport Nixon and Barker[117] reported a low platelet count in the peripheral blood and a bone marrow showing immature megacaryocytes with vacuolated cytoplasm and pyknotic nuclei splenectomy in this patient failed to stop the process Tridione[118 119] is reported as another

drug, which may cause thrombocytopenic purpura as part of a pancytopenia with the clinical findings of aplastic anemia, in one of these cases[10] at autopsy no megacaryocytes were seen in the bone marrow.

These findings suggest that the mechanism of the thrombocytopenia in the toxic group of cases is injury to the megacaryocyte itself which brings about a decreased formation of platelets. In this group *hypersplenism does not seem a probable mechanism of the thrombocytopenia* and consequently splenectomy would not be expected to be curative, some cases in which it has been tried are in accord with this idea.

More definitely of the mechanism of allergy are those patients in whom thrombocytopenic purpura occurs as part of a food allergy as has been reported with moderate frequency. Avitaminosis is stated to be another possible cause of thrombocytopenic purpura. The hemorrhagic phases of scurvy, a vitamin C deficiency, is not a thrombocytopenic purpura but results from local changes in blood vessels leading to the escape of red blood cells, this is discussed in Volume IV, Chapt XI of Oxford Medicine. An interesting example of ascorbic acid deficiency is the disease, onyalai, a form of thrombopenic purpura with prolonged bleeding time and normal coagulation time seen in Africa, this can be cured with large doses of ascorbic acid[60]. Actually since at first ascorbic acid was not available it was cured by injecting 10 to 15 c c of lemon juice in equal amounts of normal saline [illegible] or 3 times a day.

Vitamin K deficiency causes a hemorrhagic diathesis by lowering the prothrombin level of the blood, this is not to be grouped with the thrombocytopenic purpuras. Another vitamin factor in hemorrhagic conditions is the possible deficiency of vitamin P leading to an increased capillary fragility or permeability. Rapaport[3] in a study of 1[illegible] children concluded that vitamin P appears to play an important role in the mechanism of the permeability of the capillary wall. More observation and therapeutic trial are needed before assigning to vitamin P deficiency its proper place in the causation of hemorrhagic complexes.

Radiation in its various forms or radioactive substances may like intoxications already cited cause thrombocytopenia and possible purpura. X-ray, radium thorium and mesothorium have been reported as causing thrombocytopenic purpura. Now with the availability of radioactive isotopes numerous other radioactive substances may be expected to cause thrombocytopenic purpura, if given in sufficient amount and over a long enough period as already reported in the treatment of polycythemia with radioactive phosphorus[[illegible]7]. Here again vitamin P is reported to have a curative or preventive action[3,3]. How

ever there is doubt among some of the students of vitamins with regard to vitamin P and recently a group of them have advised that the term be abandoned[3, 4]

Possibly some cases of symptomatic or secondary thrombocytopenic purpura considered to be of avitaminosis etiology are either idiopathic and consequently incidental to the occurrence of this form of purpura or have some other, not recognized factor of etiology

Symptomatology

Symptomatology is the same as described for the idiopathic or essential form of thrombocytopenic purpura with as in it variations in extent and distribution of areas of hemorrhage, in accompanying general manifestations as fever, leucocytosis and anemia and in severity of illness along with the symptoms and signs of the causative or accompanying disease process

Diagnosis

As far as the element of thrombocytopenic purpura is concerned the diagnosis is made as discussed under idiopathic or essential thrombocytopenic purpura Most important in diagnosis is the recognition of the causative factor operative in each case because successful treatment depends often in very considerable measure on prompt removal of the causative factor and/or its adequate therapeutic management A very thorough history should be taken including especial attention to occupation in relation to a possible industrial hazard involving exposure to a chemical known to cause purpura on occasions and in relation to any medicament that the patient has received for in that may be found the cause of the purpura A history of previous attacks of purpura may have a diagnostic import either in suggesting an idiopathic or primary type of the disease or in pointing to a cause in that the previous attacks of purpura have occurred when a certain drug was being taken or were in relation to some infectious disease

X ray study of the bone marrow is indicated if neoplasm or sclerosis is probable not infrequently x ray will yield very important data for correct diagnosis Obviously careful study of blood and bone marrow smears is indicated in every case the existence of any primary blood disease should be recognized at once

Enlargement of the spleen is important of recognition as throwing light on a possible mechanism of hypersplenism for patients with enlarged spleen Enlargement of the spleen may escape recognition on palpation of the abdomen, sometimes x-ray will show enlargement of the spleen in patients, in whom for one reason or another the increased size of the spleen has not been demonstrated by physical examination Since enlargement of the spleen is very unusual in primary or idiopathic thrombocytopenic purpura, finding an enlarged spleen in itself is very strongly suggestive that the thrombocytopenic purpura in that patient is of the secondary or symptomatic type

It is important to recognize the presence of infection in these cases determining as far as possible whether the infection is primary and causative of the thrombocytopenic purpura or secondary and complicating in a purpura of other cause In either sequence the infection needs appropriate treatment, particularly the use of an antibiotic to which the causative organism is susceptible

In every patient with secondary or symptomatic purpura a very thorough diagnostic survey of all features of the case is imperative for, only after a complete diagnosis has been made can the proper plan of treatment be determined on since not only the purpura itself but its causative factor will need therapeutic attention

Prognosis

Many more patients with secondary or symptomatic thrombocytopenic purpura recover than die This is especially true when an early, complete diagnosis is made and appropriate treatment is instituted This of course, applies to the purpuric phase since in some of the patients although the purpura is cured, the underlying disease will progress to a fatal ending since there is no effective curative therapy available for the underlying disease Examples of this are cases of purpura in leucemia, aplastic anemia bone carcinosis Hodgkin's disease etc Omitting situations as referred to in the preceeding two sentences the prognosis in secondary or symptomatic purpura is very good

Treatment

The treatment of secondary or symptomatic thrombocytopenic purpura may be divided into two parts one part is directed to the

direct control of the purpura the other part is concerned with the control or the prevention of the action of the causative factor

This form of purpura should be controlled by using blood transfusions to restore the platelets and to control any coexistent anemia Transfusions of fresh whole blood should be given promptly as in the treatment of essential or primary thrombocytopenic purpura As purpura in these patients always is potentially if not actually a serious condition these transfusions should be used promptly in every case

In addition to transfusions, treatment should be directed towards removing or at least modifying the causative factor in each individual case Obviously this can be done only if the causative factor has been *recognized The needed therapeutic measures will vary to accord with the class or type of factor causing the existent thrombocytopenic purpura*

For those patients in whom the deficiency in platelets is due to the bone marrow changes of a blood disease the causative blood disease needs to be treated by such effective therapeutic measures as we possess The simplest of these to treat is the patient only very rarely seen in which the purpura results from very extensive bone marrow lesions in pernicious anemia vigorous parenteral treatment with large doses of a very potent liver substance or with vitamin B_{12} should be given to these As another example if leucemia is the causative lesion in the bone marrow radiation therapy is indicated If there is no effective treatment available for the blood disease as for example in true or aplastic anemia *blood transfusion which is the best measure available can be expected to have only a temporary effect*

When the causative factor is a bone marrow neoplasm radiation therapy in addition to blood transfusions should be used even though the improvement probably will be only temporary The same applies to the purpura patient with multiple myeloma In addition to radiation any probably beneficial treatment should be tried as the use of endocrine preparations and orchidectomy when there are bone metastases from prostatic cancer

When the spleen is enlarged in patients with secondary or symptomatic thrombocytopenic purpura it is probable that hypersplenism as *already discussed is the important causative factor in the mechanism of the purpura* This should be tested for with adrenalin If hypersplenism is indicated in such patients splenectomy is advisable even though the primary disease will progress and in the end be fatal

When the purpura develops in an infection or infectious disease

besides blood transfusions, vigorous treatment of them with the probably most effective specific therapy is indicated such as specific antitoxin or antiserum or that form of chemotherapy, a sulfonamide, penicillin, aureomycin, streptomycin, etc., to which the causative organism is most susceptible. Prophylaxis against purpura in these patients depends on early diagnosis and vigorous treatment of the infection or infectious disease. It would seem that on the basis of such prophylaxis thrombocytopenic purpura in patients of this group in recent years has greatly decreased.

The toxic forms of symptomatic thrombocytopenic purpura should be treated by blood transfusions and the prompt cessation of exposure to toxic product, be it an industrial hazard or a therapeutically used drug. A susceptible person should not be allowed to return to an industry using a chemical which has proved toxic to him, unless the individual can be completely guarded against any contact with it. In the same way, a drug to which the individual has been found toxic should not be used again. It is to be remembered that the individual's susceptibility, possibly of an allergic nature, is the important thing and so only a small, even a very small amount of the offending substance may be responsible for the purpuric reaction.

In addition to removal from contact with and/or discontinuance of the using of the substance which has caused the purpuric reaction, measures known to be curative of its toxic reactions and of the consequent purpura should be utilized. Examples of this are the reports of the cure of thrombocytopenic purpura caused by colloid gold[121] and by arsphenamine[11] by the use of BAL (2,3 dimercaptopropanol) and a case caused by gold cured by splenectomy.[305]

If purpura results from food allergy, the offending food substance needs to be sought out by the methods usually in use by allergists and removed from the diet and its subsequent use guarded against. If a radioactive substance is causative, contact with this should be removed or, if present in the body, its elimination needs to be increased by any effective measure that may be known.

Toluidine blue, as discussed in the section Hyperheparinemia, seems to have a place in treatment of both primary and secondary thrombocytopenia.

NON THROMBOCYTOPENIC PURPURA

In contrast to the thrombocytopenic purpuras there are numerous patients with purpura or bleedings in whose blood platelets are normal *in number and appearance The mechanism of purpura or bleedings in* these cases apparently is not caused by a deficiency of platelets or a defect in platelet participation in the mechanism of blood clotting In these types of purpura the clotting time bleeding time and type of clot formation are normal The mechanism of bleeding in these patients will be discussed in the following sections in general in these patients the vascular vulnerability factor already discussed under the heading Thrombocytopenic Purpura plays the major role while the thrombocytopenic factor has no or only a very minor role Like the group of thrombocytopenic purpuras the non thrombocytopenic purpuras can be subdivided into essential primary or idiopathic and secondary or symptomatic groups each of which again can be divided into subgroups as will appear from the following discussion

In contrast to the essential primary or idiopathic group is the group of secondary or symptomatic non thrombocytopenic purpuras These differ from the former group only in that in each case a definite cause can be assigned although for some of these patients it may be that the assigned cause is only a coincidental factor

Then there are patients usually but not always non thrombocytopenic sometimes thrombocytopenic but with various and additional factors of the mechanism of bleeding present in different patients These it seems better to group separately from the thrombocytopenic and non thrombocytopenic groups and to discuss them under various separate headings as shown in the classification appearing on an early page of this chapter These are described under the following headings Purpura Fulminans Hereditary and Familial Purpuras and Bleedings (Hemophilia Pseudohemophilia Recurrent Hemorrhage Non familial Recurrent Epistaxis Familial Recurrent Epistaxis without Telangiectasia Familial Recurrent Epistaxis with Telangiectasia Familial Recurrent Hemorrhage Other than Epistaxis Hereditary Familial Purpura Simplex) Fibrinopenia Hypoprothrombinemia Hyperheparinemia Circulating Non heparin Anticoagulants

ESSENTIAL PRIMARY OR IDIOPATHIC NON-THROMBOCYTOPENIC PURPURAS

ANAPHYLACTOID PURPURA (SCHONLEIN-HENOCH'S PURPURA)

Introduction

Of the essential non thrombocytopenic purpuras anaphylactoid purpura is clinically most interesting and of greatest importance. Here are grouped those patients formerly called Schonlein's purpura, Henoch's purpura, rheumatic purpura, peliosis rheumatica and Osler's erythema group of skin lesions with visceral manifestations. Some[3] prefer to use the term, Schonlein Henoch syndrome, instead of Schonlein-Henoch purpura since purpura is not a constant feature in them.

The term anaphylactoid generally is credited to Frank[4], but Glanzmann[5] points out that Pfaundler used the term prior to Frank[4]. Quite recently studies[1-6] have appeared which indicate that in this form of purpura there is a true allergy. Whether a true allergy or not it is a convenient grouping of patients to bring them together under this heading and it makes for a clearer clinical understanding of them.

Earlier workers such as Glanzmann believed that bacterial infection provided the foreign protein to cause the anaphylactoid reaction that constituted the disease while others have believed some substance was absorbed from the intestinal tract of a histamin like nature, still others, as already mentioned, consider it to be a true food allergy. All are in agreement as to its being of the nature of an anaphylactic or allergic reaction even if a true allergy can not be demonstrated in very many of the patients and hence the term anaphylactoid purpura seems a fairly satisfactory term to use.

Just how to group the remaining forms of purpura and other purpuric states enumerated in the Classification given in the first part of this chapter has been a matter of much discussion. There is general agreement on one point and that is that thrombocytopenia is absent or plays a very minor role in the mechanism of the recurrent bleedings in very many of these patients. Some would place them all along with patients of the preceding group, under a general heading anaphylactoid purpura. However it seems better to separate out the group of anaphylactoid purpura as a special subgroup of essential primary or idiopathic non-thrombocytopenic purpura, that has been done chiefly

because of the clinical characteristics of the group Other forms of essential primary or idiopathic non thrombocytopenic purpura have been subgrouped under the headings purpura simplex purpura senilis purpura cachectica and mechanical or orthostatic purpura As might be expected from the terms used there is a considerable overlap among these groups Some prefer to use the term purpura simplex for all of them

It is very interesting and demonstrates a great degree of clinical acumen that an association between arthritis abdominal colic and purpura and other skin lesions was recognized so early and by some very early observers distinguished from purpura hemorrhagica Willan (1808)[3] Bateman (1819)[18] d'Angers (1827)[19] Latour (18 8)[13] Schonlein (about 1830)[131] all reported observations of patients with such lesions Henoch's report[13] was made in 1874 Osler's contribution[133] beginning with 1895 was to call attention especially to the protean nature of the skin lesions often with variation in type from attack to attack

Pathological Physiology of Anaphylactoid Purpura

Unlike other purpuras as already indicated it is characteristic of the anaphylactoid purpura group to have numerous manifestations of the disturbance in the skin and also in the joints and internal viscera especially in the gastrointestinal tract[131, 13] The common factor in all of these disturbances is a lesion of unknown cause in the small blood vessels possibly the capillaries which results in congestion hemorrhage or exudation singly or in different combinations Morphologically the blood is unchanged from normal rarely there is sufficient blood loss to lead to the picture of severe secondary anemia blood platelets are unchanged it is a non thrombocytopenic anemia Bleeding time and clotting time are normal The clot is normally retractile The process of coagulation is normal Blood chemistry is normal

Certainly there is great similarity in this condition to certain observed sequences of anaphylactic reactions and of serum sickness Latterly as already mentioned cases have been described[1, 18] in which a definite food allergy is responsible for the attacks Probably it is going too far to say that all cases have this origin However to look upon them as anaphylactic or anaphylactoid manifestations surely facilitates our understanding of them

It seems to me[131] that the subject is somewhat clarified further by looking on all of these patients as having in common focal disturbances that allow of various types of exudation, giving skin lesions of different appearance, depending on the relative proportions of serum, red cells white cells and tissue reaction and visceral lesions of different sorts *depending on the site and character of the visceral vascular lesion* This conception would explain the varying skin lesions now with arthritis now with abdominal pain now with hematuria, etc, in all sorts of combinations

As far as the skin lesions are concerned, there are many names as there are many surface appearances Purpura simplex, Henoch's purpura Schonlein's purpura purpura rheumatica, peliosis rheumatica erythema simplex erythema multiforme, erythema multiforme bullosum erythema multiforme vesiculosum, erythema iris erythema urticans erythema nodosum erythema papulatum erythema pustulosum herpes iris urticaria uticaria pigmentosa and angioneurotic edema are some although not all of the names used by the dermatologist for a group of conditions which have in common focality and various combinations of dilatation of and exudation from, small blood vessels now of serum now of red cells now of white cells but usually combinations of these various processes with which frequently are associated visceral disturbances It would seem to go too far to regard all of these as manifestations of a single process Still, as these various skin lesions do occur in association with certain general disturbances and as the exact form of skin lesion may vary from time to time in the same individual it seems simpler to regard them as part of a general process rather than merely as local skin lesions but we should not deny that the same skin manifestations may, and often do, appear as purely local skin processes In these various respects they may be discussed as a fairly definite clinical entity

Exudation of various sorts into the intestinal wall may occur The ...dix, so distended produces the symptoms of appendicitis and be removed at operation in the belief that an acute inflammatory is present The thickened intestinal wall interferes with peris... l constipation, colic or intestinal obstruction result Blood and ...ping into the lumen leads to diarrhea often bloody, or merely to ... hemorrhage frequently severe Similar changes in the ... nausea and vomiting sometimes bleeding Foci of hemo... ...ur in the kidney and result in hematuria Albumin escapes, ... is albuminuria Edema of the kidney depresses renal

function Casts are found and it is extremely difficult to tell whether there is an acute nephritis or not Nephritis of different varieties not infrequently develops and patients are described in whom the renal process progressed to an eventual uremia Blood may clot in the renal pelvis and in efforts to expel the clots renal colic results simulating that from calculus Serous exudate into joints causes arthralgia and often simulates arthritis These changes may lead to actual tissue reactions producing chronic arthritis such as occurs in hemophilia Uterine hemorrhage may simulate that of local disease such as hyperplastic endometritis fibroid or cancer These resemblances to various forms of disturbances which the surgeon deals with by operation become very important because so often mistakes are made in diagnosis and needless operations are performed The group with the combination of purpura arthritis and abdominal pain is frequent and is very generally spoken of as Henoch s purpura but even in the most typical cases in some attacks instead of purpura the skin lesions are of the erythema or urticarial type which renders unsatisfactory the term Henoch s purpura Purpura rheumatica or Schonlein s purpura are still more unsatisfactory terms

Clinical Features of Anaphylactoid Purpura

Some idea of the clinical picture is given by the following cases which have come under my observation at the Peter Bent Brigham Hospital

Case 1 (Peter Bent Brigham Hospital Med No 5016) — Purpura abdominal pain blood in the stools A woman aged forty five two weeks before admission noticed red spots on the legs below the knee and then they appeared on the hands forearms and lower abdomen Those on the arms itched slightly They varied in size from a pinhead to 0 5 cm in diameter at first bright red and then turning a darker red and gradually fading On the day of admission a slight swelling which was red and quite tender appeared on the left instep and two days later a slightly painful lump appeared in the middle of the forehead about 3 cm in diameter which was raised about 0 5 cm above the level of the forehead At this time pain began to develop in her legs The next day her left knee was painful on motion and her left ring finger was swollen at the second phalangeal joint The left shoulder joint was tender on palpation The patient had a very slight fever A day or two later the patient had an attack of vomiting at night and on the next day there was a new crop of skin lesions more papular than previously and more numerous on the face The joint pains persisted for four

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Exudation of various sorts into the intestinal wall may occur The appendix, so distended produces the symptoms of appendicitis and may be removed at operation in the belief that an acute inflammatory process is present The thickened intestinal wall interferes with peristalsis and constipation, colic or intestinal obstruction result Blood and serum escaping into the lumen leads to diarrhea often bloody or merely to intestinal hemorrhage, frequently severe Similar changes in the stomach cause nausea and vomiting, sometimes bleeding Foci of hemorrhage occur in the kidney and result in hematuria Albumin escapes, and there is albuminuria Edema of the kidney depresses renal

abdominal pain painful swollen joints Three and one half weeks before the patient a girl aged eleven came to the hospital a rash appeared on the back of the calves and over her lower legs which gradually went up the legs and a few appeared on the trunk Finally a rash appeared on her face The rash was red in color and consisted of discrete sharply defined macules During the first three days after the rash appeared the patient vomited frequently yellow greenish material free from visible blood During this time her stools were dark colored One week after the rash appeared her ankles became swollen and two days later swelling appeared in her hands This swelling in the hands and feet disappeared but occurred again later When the patient came to the hospital there was slight abdominal tenderness there was a marked macular and papular rash over the legs feet and arms in places dark red in other places paler purplish or yellow in color On one ankle there was a bleb about the size of a dime At this time there was no obvious involvement of any joint After two days in the hospital the patient had a stool in which there was bright red blood and a little later she involuntarily passed about four c c of blood The next day there was diarrhea with several watery stools most of which showed blood On this day the right hand and arm as high as the elbow were distinctly swollen but not very tender Several days later there was a recurrence of the diarrhea there being very numerous stools most of which contained blood This persisted for several days and then diarrhea gradually decreased though positive guaiac tests continued to be obtained in her stools for a long time

After being in the hospital for a month a new crop of purpuric spots appeared on her feet Four days later a new crop came on her legs A week later she again had pain in her abdomen and vomited Shortly afterward she passed a large tarry stool She remained in the hospital for nearly four months with frequent recurrences of what has been outlined already and then left in good condition She was seen a year later and reported that she had had a few purpuric spots in the interval but no recurrence of the diarrhea and abdominal pain

Case 4 (P B B H Med No 3599)—Purpura painful joints hematuria A man aged twenty five about two weeks before admission developed a sore throat Five days ago his knees became a little painful on motion and after resting would feel stiff For two days his feet have been a little swollen Nine days ago his feet became tender and were painful when he walked about On yesterday he had a little trouble pulling on his boots and later in the day noticed that there was a red rash about his ankles When he came into the hospital on both ankles and over the calves of both legs there were many dark red hemorrhagic areas from 0 5 to 8 mm in size A few of these were covered with fine crusts Both tonsils were enlarged red and slightly ragged The urine contained a moderate amount of albumin and numerous hyaline and granular casts A specimen of urine passed

to five days varying in intensity Two weeks after admission she complained of extreme pain in the lower portion of the abdomen The abdomen was markedly distended more or less rigid and was tympanitic throughout The pulse became smaller the heart sounds were weak but she had no fever at this time She was given several high enemas and the pain gradually disappeared though the distention persisted somewhat longer Two days later however the abdomen felt perfectly normal and the pain had disappeared entirely from the abdomen A number of stools examined from the time of admission up to this period of abdominal pain showed strongly positive guaiac tests Then the stools became negative for blood tests and thereafter for a period of nearly a month the guaiac tests were sometimes positive sometimes negative During this period the patient s condition greatly improved and she left the hospital feeling comparatively well During her stay in the hospital albumin was found occasionally in her urine, and an occasional cast was seen but there was no hematuria

Case 2 (P B B H Med No 1143) —Purpura abdominal pain pain and swelling of the ankles hematuria A boy aged thirteen about six weeks before admission was seized suddenly with sharp cramp like pain in the abdomen, more severe about the region of the umbilicus This pain did not radiate and it lasted for about ten minutes Since then there have been many recurrences of similar paroxysms of abdominal pain and he has never been free from the sensation of discomfort in the abdomen during this time When the pain is severe, he occasionally vomits a small amount This vomiting is not preceded by any nausea The first two urine specimens examined in the hospital showed numerous red blood cells subsequently none were found The patient was distinctly emaciated his abdomen had a doughy feel Roentgen ray studies of his gastrointestinal tract showed distinct irregularities in the pyloric and prepyloric region The stomach emptied rather slowly When the opaque mass reached the small intestine, the loops looked wide and atonic While in the hospital the patient frequently had attacks of very intense abdominal pain which would double him up and sometimes he would vomit At times food taken several hours previously was found in the vomitus Ten days after the first bismuth Roentgen ray examination a repetition showed again irregularity in the prepyloric region with a slow emptying time for the stomach After two weeks stay in the hospital the patient began to improve his colic like pains decreased his appetite improved and he looked very much better After nearly a month in the hospital there was a recurrence of pain in the abdomen followed the next day by pain and swelling in the right ankle A day later several purpuric spots appeared on the legs These gradually faded away not to recur During the latter part of his stay in the hospital a small amount of blood reappeared in the urine and albumin was present with an occasional cast

Case 3 (P B B H Med No 1069) —Purpura diarrhea blood in the stool

area with a little black speck in the center About five days ago blisters appeared in the mucous membrane of his mouth On admission he showed over the mid portion of his right lower jaw an irregular area of yellow crusts Irregularly scattered over the arms and legs there are small areas of erythema with blackish brown spots in their centers Over the back of his thighs there are a number of red areas some almost entirely covered with blebs containing a serous fluid The edges of these areas are sharply demarcated Over the palms of the hands and the soles of the feet are a large number of blebs varying in size from a ten cent piece to a twenty five cent piece When the blebs break it is seen that the lesion as far as ulceration is concerned is very superficial On the lips there are similar blebs and apparently they have occurred also on the gums appearing here as erythematous areas slightly ulcerated These lesions rapidly cleared during about ten days stay in the hospital The patient's urine was normal and there was no blood in the stools

Case 7 (P B P H Med No 5661) — Erythema multiforme vesiculosum abdominal pain Eleven days before admission in a woman aged twenty nine generalized pain in the abdomen developed This began in the morning and got worse in the afternoon During the night it was severe enough to prevent sleep Her local physician saw her the next day and diagnosed the condition as salpingitis He prescribed a vaginal douche and after a few days the pain subsided Then the pain recurred and she went to a dispensary where she was diagnosed as having gallstones With this attack she vomited and continued to vomit until she was sent to the hospital where she was first admitted on the surgical side There it was found that she had an irregular blotchy erythematous eruption over her face and almost the entire body These erythematous areas did not seem to be elevated and they faded on pressure The abdomen showed generalized tenderness Her feet and ankles were swollen and tender In twenty four hours the skin rash had disappeared largely leaving a slight puffiness of the face hands and feet The rash reappeared and a week later a different type of rash appeared on the arms and legs consisting of small irregular dusky red areas 2 to 6 mm in diameter which did not disappear on pressure On the tops of many of these lesions small vesicles appeared which subsequently became slightly pustular The patient now complained of abdominal tenderness and there was slight diarrhea The urine showed a slight amount of albumin numerous casts and a phthalein output of fifteen per cent in two hours which in two or three days had increased to twenty four per cent and a week later to thirty four per cent The patient had a moderate degree of irregular fever At times the pain in her elbow and wrists became more severe and kept her awake After being in the hospital for nearly a month she had a recurrence of the pain in her abdomen and the left arm from the elbow to the shoulder became swollen and tender and felt hot but it was not red This

nearly two weeks after admission was smoky and contained many red blood cells This was at a time when the throat had cleared up and the purpura had disappeared After about three weeks in the hospital and when the patient had been up out of bed for three days purpura returned over the ankles with slight pain and swelling in the ankles The blood was very slight in amount in his urine at this time but ten days later became more abundant This patient had a positive Wassermann reaction and there was an ulceration in the palate Renal function was slightly impaired as shown by the blood urea nitrogen which was 25 mgm per 100 c c of blood with an index of urea excretion according to McLean s formula of 40 5 per cent Some time later the blood urea nitrogen was 21 mgm with an index of urea excretion of 49 per cent The phenolsulfonephthalein test at about this time gave an excretion in two observations of 67 per cent and 50 per cent respectively and the urine always contained a considerable amount of albumin and numerous casts hyaline and granular in character so that the diagnosis of acute nephritis was made also though this may have been in correct

Case 5 (P B B H Med No 5372) — Erythema nodosum abdominal pain, vomiting slight diarrhea A woman aged twenty-seven for about four weeks had had grumbling pains in the left upper quadrant of the abdomen On two occasions she vomited and for several periods of about a week there was slight diarrhea Nothing abnormal was noted about the vomitus no blood was observed in the stools A few days ago the patient felt rather chilly and went to bed The following morning after walking down stairs she noticed soreness in both legs from the knee to the ankle That night she noticed what she called mosquito-bite like areas over both lower legs Two mornings ago these seemed to be fading but by today had become larger and felt lumpy During this period there has been slight sore throat When she came to the hospital there were numerous discrete lesions over both legs These lesions were slightly raised reddish blue or slightly yellow in color with ill-defined edges measuring from 1 to 4 cm in diameter On palpation they give a distinctly nodular feel On pressure most of the color disappeared from the lesions When she came in there was slight fever which quickly disappeared All the gastrointestinal symptoms likewise dis appeared Her urine examination was normal

Case 6 (P B B H Med No 5543) — Erythema multiforme bullosum gastric disturbance A boy aged thirteen for the past five years every August has had a gastric upset with an erythema on the right side of his lower jaw This usually lasts five to six days Eating strawberries often produces a little urticaria and on one occasion he had urticaria from eating fish About a month ago the same appearance as usual occurred on his jaw Then red spots appeared on his legs and arms Soon a blister would form over these red spots which would break in about twenty-four hours leaving a red

which pus exudes on pressure Six days before he came to the hospital he began to have a sensation of pressure in the epigastrium giving him enough distress to keep him awake during the night He raised a good deal of gas Four days ago he began to have hiccups and to vomit about once or twice an hour There was very little nausea. The vomitus was bitter greenish in color and never contained anything like blood

On admission numerous small purpuric spots were found over both elbows and over the lower part of the sacrum which he says had been present for three to four days A carious tooth was found as described The left knee was somewhat larger than the right, somewhat painful not hot and did not appear to contain fluid His left leg was slightly flexed at the knee and held in that position He had a moderate fever During his first few days in the hospital the urine contained a very slight amount of albumin with a few hyaline casts The phthalein elimination was forty two per cent in two hours In his stools a strongly positive benzidin test for blood was found The pain in his knee decreased and then after four to five days increased and at this time there appeared on the forearms wrists legs ankles and feet many small slightly indurated erythematous plaques definitely elevated and about 1 cm in diameter These gradually disappeared and a week after this crop had come out the patient s temperature suddenly rose to 10 F and there was marked swelling of the left knee and a re appearance of purpuric spots on the forearms ankles and feet Now there were definite signs of fluid in the knee joint The patient was unable to flex his knee on account of pain At this time the bad tooth was extracted and pus was found about its root

For the next two weeks the temperature ranged between 99 and 100 F Then it rose again to 10 , F with a fresh crop of purpuric spots on the forearms ankles and feet The patient had begun to cough up a considerable amount of blood During this time a small amount of blood had appeared in his urine and the casts had increased in number Shortly after this last group of purpuric spots appeared the urine became definitely hemorrhagic in type and thereafter contained practically always a con siderable amount of blood though different specimens might show more or less blood A guinea pig inoculated with urinary sediment was negative for tuberculosis After a month s stay in the hospital the patient had a definite secondary anemia but he had been free from purpuric attacks for some little time blood in his stools was no longer found and the blood in his urine had somewhat decreased Roentgen ray examination of his knee shortly after this showed bony enlargement and slight irregularity but no evidence of a destructive process Now the patient s temperature became a maintained temperature first around 101 F and then increasing to 10 F and finally rising to about 103 F with a gradually increasing pulse rate During this period the left knee continued swollen and painful with some

swelling gradually subsided and the tenderness disappeared From time to time the patient had a severe headache She gradually improved and left the hospital feeling quite well after a stay of about two months Before she left her 'phthalein excretion had risen to fifty five per cent

Case 8 (P B B H Med No 5908) —Urticaria intestinal obstruction The patient a man aged fifty-eight had had a large number of attacks of localized swelling in the right hand and other manifestations of urticaria On the day before coming to the hospital he was in his usual health until the after noon While having tea his abdomen became distended, there was some belching of gas he felt rather uncomfortable and went to bed He began to have pain in his abdomen chiefly in the epigastrium and along the right costovertebral angle His abdomen was generally distended There was a fair bowel movement about 9 P M Later an enema was given and returned with very little fecal material The distention and discomfort continued so that he slept poorly The next morning January 7 he came to the hospital and his abdomen was found to be distended and diffusely painful and slightly tender The abdomen and the character of the pain suggested distinctly intestinal obstruction For twenty-four hours very little result was obtained from enemas or rectal tube then a good fecal result was obtained and the patient passed a considerable amount of gas Forty eight hours after admission his abdomen was much less distended and the patient was much more comfortable Four days after admission scattered patches of erythema and edema appeared over his hands arms and feet which he said were similar to those that he had had repeatedly after eating fish shellfish or canned goods that were possibly not quite good He recalls having eaten sardines on the day that his abdominal distention and discomfort developed These findings suggested that possibly the intestinal obstruction was due to a similar type of lesion in the intestinal wall and on the next day, January 12 roentgen rays of his gastrointestinal tract showed five hours after the taking of the opaque meal in one of the upper loops of the ileum a dilatation producing a sausage-shaped shadow the distal end of which was narrow After this all symptoms of intestinal obstruction disappeared a repetition of the roentgen-ray study three days later showed no signs of a dilated loop and a repetition ten days later again gave no evidence of obstruction

Case 9 (P B B H Med No 58-3) —Purpura arthritis abdominal pain hematuria blood in the stools A man aged twenty, six years ago had an attack of rheumatism in which both knees were slightly swollen and quite painful, particularly at night Since then he has had a similar attack about once a year About nine weeks ago another attack of rheumatism developed in which his right knee became sore A little bit later his left knee became very painful and slightly swollen The right knee cleared up but the left knee continued and still is swollen and painful For a year the patient has had an ulcerated tooth in the right lower jaw with a swelling nearby from

in all 12 cases and intestinal symptoms in all but 1 11 had colic 8 blood in the stools and 6 had vomiting Articular symptoms from transient puffiness of a single joint to recurrent painful swelling of many joints occurred in 10 of the 12 patients All except 1 patient showed some renal involvement with gross hematuria in 4 and microscopic in 7 Subsequent history showed that the renal lesion might go on to recovery to latent nephritis to chronic nephritis or to rapidly developing renal failure and death Gairdner believed that the Schonlein Henoch syndrome acute nephritis rheumatic fever and polyarteritis together made up a family of diseases with blood vessel involvement in Schonlein Henoch syndrome the small vessels of the skin intestine synovia or glomeruli in nephritis the glomerular capillaries in polyarteritis nodosa the medium sized arteries and arterioles and in rheumatic fever probably connective tissue damage secondary to vascular lesions He believed the pathogenesis common to this group is probably an antigen antibody reaction taking place especially in the endothelium of certain blood vessels the antigen usually being a derivative of the hemolytic streptococcus

Diagnosis of Anaphylactoid Purpura

The association of a history of skin lesion with visceral symptoms the search for skin manifestations when the visceral crises are prominent the remembering that visceral manifestations may precede skin lesions and are to be thought of when fever is absent and the fact that the visceral symptoms have no obvious cause are the means of preventing errors in diagnosis errors which at times lead to unneeded and unavailing operations At best errors in diagnosis will occur The absence or slight degree of fever the absent or slight leucocytosis usually present in this group aid in distinguishing the symptoms from those caused by inflammatory processes In some cases however both fever and leucocytosis are present The intestinal lesion may lead to an actual intussusception with intestinal obstruction or cause a local necrosis with perforation both requiring prompt surgical treatment if life is to be saved On the other hand often the diagnosis of a condition requiring operation is made on the basis of the abdominal symptoms and an unneeded operation is performed It is not easy to steer a safe course between these two dilemmas

It is easy to confuse these patients at times with rheumatic fever or

variation up and down in the activity of the process After about two and one-half months' stay in the hospital with this continued fever, continued hematuria and continued activity of the process in the left knee, definite signs were made out of a pulmonary process and tubercle bacilli were isolated from the sputum in small numbers A month prior to this, sputum examinations had shown no tubercle bacilli A roentgen ray plate of the chest showed changes suggesting a diffuse miliary tuberculosis with in places conglomerate tuberculosis There were no further crops of purpura and the patient died about three and one half months after admission At necropsy there was an acute miliary and conglomerate tuberculosis of the lungs with areas of caseous pneumonia apparently an active and recent tuberculous process The kidneys were slightly enlarged and showed small foci of hemorrhage On microscopic examination of the kidneys there was no nephritis but possibly a slight degenerative change in the tubular epithelium with numerous foci of intertubular and intratubular hemorrhage explaining the persistent hematuria No tuberculous lesions were found in any of the abdominal viscera The gastrointestinal tract seems to be normal The stools for a period of three months before death gave no test for blood

These cases illustrate very well the admixture of skin lesions, abdominal symptoms and arthralgia or arthritis, which is characteristic of the disease Any one of these symptoms may occur first, and there is no constancy as to their sequence or time relations Recurrence of any of the group is apt to take place With active symptoms, constitutional disturbances are the rule as malaise, headache fever diarrhea nausea and leucocytosis In some cases, as in one reported from my clinic by George H Herrmann[135] fever may rise as high as 104 F *with a* leucocytosis up to 42 000 and simulate a septic condition

The skin lesions as already seen, may vary much in type, although a purpuric rash is seen most often Ankles and knees are the joints most often involved Usually swelling is slight, although at times hydrops develops in the joint The abdominal pain is apt to have a colicky character and may be localized in any part of the abdomen Constipation may be present to be followed by diarrhea Blood often appears in the stools Nausea and vomiting are frequent The urine, as a rule contains some albumin and casts Often red blood cells are present Not infrequently the picture is that of acute nephritis In some chronic nephritis ensues With hematuria there may be pain of a renal colic type from the passage of blood clots

Gairdner[2 0] recently (1948) reported a study of 12 cases of the *Schonlein Henoch syndrome These with 2 exceptions were* children between 4 and 15 years old, 10 were males A skin rash was present

TABLE I

	Anaphylactoid Purpura (Schönlein Henoch's Purpura)	Thrombocytopenic Purpura (Werlhof Disease)
Onset	in connection with known or unknown infections or with allergy	appears in those primarily well
General symptoms	infectious toxic symptoms — lassitude, headache, loss of appetite, coated tongue, fever (often sub-normal temperature)	fever only secondary to infection complicating hemorrhages
Special features other than hemorrhage	urticaria, edema, swollen joints, rheumatic pains, polyneuritis, intestinal colic with vomiting and melena, hemorrhagic nephritis	lacking
Skin lesions	petechiae usually small but rarely quite large; also urticarial and erythematous exanthems	in addition to petechiae large areas of purpura with changing color as the lesions fade
Localization of skin lesions	especially in extremities near joints and often symmetrically placed with head generally spared	irregular, frequently on head, not symmetrically placed; frequent subcutaneous and intramuscular hematoma; trauma often determines localization
Hemorrhages from mucous membranes	rare	frequent from nose and mouth, also conjunctival ecchymoses, often on gums and mucous membranes of mouth; hemorrhage from stomach, intestines, larynx, kidney, bladder and uterus
Bleeding time	normal	delayed
Coagulation time	normal	normal
Retraction of clot	normal	decreased
Coagulation	normal	normal
Blood morphology	neutrophilic leucocytosis and eosinophilia	inclination to leucopenia and lymphocytosis
Platelets	increased in chronic intermittent cases, slightly decreased in acute and fulminating cases	marked platelet deficiency with giant forms and pycnosis

with scorbutus The latter should be separated easily by the absence of many characteristic features and by the absence of any food deficiency when the history of the patient is obtained As to the former sometimes time alone will make the differentiation, particularly the absence of development of cardiac lesions so common following rheumatic fever

Table I, adapted from Leschke and Wittkower, will be helpful in separating thrombocytopenic from anaphylactoid purpura

Prognosis of Anaphylactoid Purpura

In this group prognosis is very uncertain Many cases have repetitions of the symptoms, sometimes over a long period of years Individual attacks usually are of from one to six weeks' duration with remissions and exacerbations of some or all of the symptoms and changes The condition rarely is fatal unless complications such as tuberculosis or nephritis develop There is no way of judging, when seen in the first attack, whether there will be recurrences or not This is not a fatal disease unless as rarely occurs a progressing renal lesion develops which eventuates into a uremic death

Treatment of Anaphylactoid Purpura

There is no specic treatment General hygienic methods to build up the patient's general condition are indicated Skin tests for protein sensitivity may explain an occasional case and give the proper therapeutic hint as in some of the cases reported by Alexander and Eyermann[1] and by Kahn[16], where skin tests showed a reaction with certain food proteins However more frequently skin tests were all negative in their patients but the causative food could be found by a process of elimination When the causative protein was discovered, its re use would cause part or all of the previous symptoms thus giving further proof of a causative relationship By applying carefully the methods used in studying various forms of allergy, it now seems possible that the cause of symptoms in more of these patients may be found, and the proper dietary regime established to prevent recurrence of symptoms As in asthma, it is not likely that only food proteins will be found responsible, and in many patients it probably will be impossible to determine a causative factor

garded to be such and these properly are classified under essential non thrombocytopenic purpura Many of them however occur in definite sequence to known debilitating usually chronic disease and so should appear under symptomatic or secondary non thrombocytopenic purpura As there seems to be no essential difference recognizable in these cases they will be discussed as a group with no attempt to distinguish essential from secondary types Then too there is no sharp demarcation between these and the purpura following acute infections with or without thrombocytopenia Finally the latter are related closely to the purpuric phases of the skin lesions of the various acute infectious diseases such as small pox vaccinia scarlet fever measles cerebrospinal meningitis typhus Rocky Mountain spotted fever tsutsugamushi fever subacute endocarditis etc In all of these at times the platelets are reduced at times normal in number although in the hemorrhagic forms of the acute exanthematous diseases blood studies in regard to platelets bleeding time clot retraction etc are not numerous enough to justify positive statements as to the frequency and variety of changes in the blood other than that a much decreased platelet count is found in hemorrhagic small pox Mechanical forms of purpura too may be grouped here since a mechanical element may appear in any of these several forms Clinically there is little difference between these patients and those who by reason of platelet deficiency would be grouped as thrombocytopenic purpuras

The cachectic forms hardly justify any attempt to differentiate them from the secondary ones Cachexia itself is too vague a term anyhow for modern use Purpura may develop during many of the chronic diseases usually in the late stage Of all it is said to be most frequent in chronic nephritis possibly because chronic nephritis occurs frequently However I have been struck by the great infrequency of purpura among my nephritis patients especially during the past twenty years while during this time I have seen it far more frequently in leucemia and aplastic forms of anemia both relatively rare diseases Chronic jaundice of any cause often develops purpura Cancer chronic heart disease Hodgkin s disease senility are other conditions in which purpura sometimes occurs

In these forms purpuric spots are more common on the legs and position may play some part in this However often it occurs on the legs in bedridden patients so scarcely could be mechanical Possibly here the poorer circulation in the legs may be a determining factor However there are patients with so definite a relation to position as

I am skeptical of the value of the much used calcium chloride or lactate It can do no harm and so may be tried In cases with an urticarial basis 1 c c of 1 to 1 000 epinephrine solution subcutaneously may be very effective Various antihistaminic drugs are worthy of critical trial[3 6] ACTH has been used Salicylates aromatic sulphuric acid oil of turpentine and ergot are advised, just why I cannot see It seems wiser to me to give nothing than to try such measures

Purpura Simplex

The term, purpura simplex seems worthy of retention although some authors have given it up By it we mean purpura without any visceral disturbances and with no known allergic relationships developing in previously well people With no allergic relationship it is not to be grouped with anaphylactoid purpura In purpura simplex there are no recognized abnormalities of the blood, certainly none to justify inclusion under thrombocytopenic purpura (purpura hemorrhagica) It would seem probable that the cause lies in some capillary abnormality Cases that show just purpura and nothing more are to be called purpura simplex This is a fairly frequently occurring type of purpura Heredity and familial incidence has been reported (see section on Heredity Familial Purpura Simplex on a later page of this chapter)

Purpuric spots in these patients usually are small and generally occur on the extremities especially the legs but they may appear anywhere on the body and at times the spots are large As a rule, there is no fever, but occasionally there is moderate fever, rarely slight leucocytosis slight albuminuria malaise and nausea to suggest some slight infection The attack may last only a few weeks but may be prolonged by recurring crops of purpuric spots even to several years, justifying our speaking of a chronic type of simple purpura Hayem according to Pratt[3], had a patient with attacks recurring over a period of ten years In my earlier clinical days I saw such patients more frequently than in later years

Purpura Senilis Purpura Cachectica Mechanical (Orthostatic) Purpura

The proper grouping of these cases is uncertain For some of them there seems to have been no underlying disease unless old age is re

Classification

Causes of this type of purpura or bleeding can be subdivided into 1) infections or infectious diseases 2) intoxications and drug idiosyncrasies 3) various chronic diseases 4) endocrine and nervous diseases 5) allergy 6) avitaminosis 7) radiation

Pathological Physiology

The pathological physiology of these cases can be explained on the basis of some change in the blood vessels by which either they bleed very easily or fail to contract as do normal vessels after any injury to them What has been termed on earlier pages of this chapter the vascular vulnerability factor is concerned in the mechanism of their bleeding

Etiology

As already indicated the etiology is various ranging from infections and infectious diseases to radiation effects In some patients the cause is definite as in the group of intoxications and drug idiosyncrasies in many of which the purpura or other bleeding will follow repetition of the cause and also as in the allergy group indicated by a positive skin reaction following application of the assigned cause In many however the relationship is inferential rather than definite this is true of the groups of infections and infectious diseases various chronic diseases avitaminoses and radiation where the sequence is frequent enough as statistically to point to cause and effect and where following successful treatment or removal of the assigned cause no repetition takes place Even though only inferential the causal relationship is highly probable justifying the grouping of these patients as secondary or symptomatic However when it comes to endocrine and nervous disease causes the causal relationship can be said to be only probable and very possibly coincidental these cases are included since from time to time reports appear claiming a causal relationship of purpura or bleeding to endocrine or nervous diseases

In the discussion of secondary or symptomatic thrombocytopenic purpura will be found enumerated the various causative infections infectious diseases intoxications drug idiosyncrasies and radiation

to justify the terms, mechanical purpura or orthostatic purpura, and other mechanical factors, such as epileptic seizures and paroxysms of whooping cough are described as causing the appearance of purpuric spots Patients are described in which a purpuric rash recurred on the legs as a result of sitting up in a chair, or where bandaged portions of the leg remained free of purpuric lesions while they appeared on un bandaged parts Possibly an incidental hypertension is causative All of this suggests a relationship to the purpuric spots brought on below a tourniquet, the so called Rumpel-Leede's test, and a relation to an increased venous pressure

Von Horvath[11] has found that in suddenly assuming the erect from the reclining posture considerable decrease in platelets takes place In a patient who had exhibited previously the phenomenon of orthostatic purpura the platelets fell from 116,000 to 23 000 and from 93,000 to 17,000 on separate occasions but no purpura resulted In normals a proportionate fall takes place but from a much higher level This drop may be an important factor in causing in some individuals an orthostatic purpura, when their reclining platelet count is low but well above the level considered critical for purpura and on standing falls below the critical level

Post-Infection Purpura

Post-infection purpura is seen after a variety of infectious diseases and as already stated there is little clinical difference between those in the thrombocytopenic and non-thrombocytopenic group The larger number of these cases are in the latter group

Secondary or Symptomatic Non Thrombocytopenic Purpura

In this group can be placed patients whose history points to a cause for the purpura or bleeding Their blood counts are normal unless blood loss has been great enough to cause anemia, platelets are normal in number or only moderately reduced The various factors concerned in blood clotting are found to be normal or only very slightly changed In these respects they are like the patients grouped as having primary, essential or idiopathic non thrombocytopenic purpura

Classification

Causes of this type of purpura or bleeding can be subdivided into 1) infections or infectious diseases 2) intoxications and drug indiosyncrasies 3) various chronic diseases 4) endocrine and nervous diseases 5) allergy, 6) avitaminosis 7) radiation

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In the discussion of secondary or symptomatic thrombocytopenic purpura will be found enumerated the various causative infections infectious diseases intoxications drug idiosyncrasies and radiation

effects All of these, so far as is known, also can cause non thrombocytopenic purpura or bleedings, they need not be repeated here as the reader will find them enumerated on preceding pages

Clinical Findings

Clinical findings in these patients are just the same as already described for various forms of essential primary or idiopathic non thrombocytopenic purpura

Treatment

Treatment of this form of purpura primarily should be removal or stopping of contact with the cause whenever that is possible The sicker patients need bed rest Transfusions of blood plasma have not proven effective in most patients, unless there is definite anemia, when blood transfusions will help Rarely one of these patients does lose so much blood that a fatality follows notwithstanding repeated blood transfusions The great majority of the patients, however, in so far as the purpura or bleeding is concerned have an excellent prognosis Various forms of drug therapy, which have been used including calcium and snake venom probably do no good and are not advised

Purpura Fulminans

This is an acute form of purpura, usually of very short duration often 18 to 48 hours, occurring oftenest in childhood frequently in infancy Often fatal in the past, if part of, and probably caused by, a coccic infection penicillin now frequently cures[140] The purpura usually is widespread It seems reasonable to include patients in whom hemorrhage from mucous membranes occurs, although Henoch himself excluded them Guelliot[136] in 1884 reported the first case, but the name was given by Henoch[137] in 1886 It has an analogue in the hemorrhagic types of the acute exanthems especially in small pox and scarlet fever, which often run a rapidly fatal course Frank, as cited by Pratt[7], believes that both in hemorrhagic smallpox and in purpura fulminans there is a combination of thrombocytopenia and capillary toxicosis Ikeda[138] finds in hemorrhagic smallpox a persisting low platelet count a

decreased polynuclear count and an increase in lymphocytes In some cases of purpura fulminans the polymorphonuclear neutrophiles as well as platelets have been found diminished but in the cases studied by Risel[139] and Elliott[140] neither one was decreased however Boettinger[141] found the platelets [illegible]1 600 in his patient Some of these cases of purpura fulminans are to be grouped as essential or primary while others should be put in the symptomatic or secondary group of non thrombocytopenic purpuras With the frequency of association with bacterial infections particularly meningococcic more are in the latter than in the former group but as except for this the cases are essentially similar they will be discussed here under the general heading of essential or primary non thrombocytopenic purpura and only mentioned for completeness sake again under symptomatic or secondary non thrombocytopenic purpura

Morawitz[34] has reported a case in an adult Elliott[140] includes 4 *adults in his 56 collected cases Pratt s*[5] *patient also was an adult but* his description suggests agranulocytosis following infection

A purpuric rash is common in meningococcus septicemia Le Bourdelles[143] recovered the meningococcus in [illegible] or 6 cases of purpura one of which was fulminating and Battley[144] and Elliott and Kaye[14] have reported [illegible] cases of purpura fulminans with the isolation of the meningococcus In recent years numerous cases of meningococcus infection with hemorrhage into the adrenals and purpura have been reported under the title Waterhouse Friderichsen syndrome This is discussed in Chapt IV A of this volume of Oxford Medicine[145] there numerous additional references will be found These cases should be considered to be a form of purpura fulminans The etiology of some of them can be demonstrated quickly by finding the cocci in leucocytes in stained blood smears[144a] Streptococci (Konig[146]) and gonococci (Brunsgaard and Thyotta[147]) too have been isolated The Waterhouse Friderichsen form of purpura fulminans also can be caused by pneumococci hemolytic streptococci and staphylococci[148, 149] The frequency following scarlet fever indicates a streptococcic relationship Should such patients be grouped as purpura fulminans along with those of unknown etiology It would seem better to do so since clinically they all are very similar

Purpura fulminans is an infrequent type of purpura Elliott[14] in 1909 in addition to his own patient found 55 in the literature which agreed fairly well in their characteristics although the 4 in his list

that recovered would not have been included by some of the observers Some, too would exclude the 4 adults In Elliott's group mucous membrane hemorrhages occurred in 18, from the nose 12, from the mouth 4 from the stomach 3 from the intestines 4 from the genitourinary tract 4, from the conjuctiva 2 and from the lungs 1 In the fatal cases the average duration from the appearance of the purpura to death was 5-½ hours 19 died within 24 hours In 20 autopsies cerebral hemorrhage was found 3 times In 22 of the cases collected by Elliott acute infectious diseases are regarded as predisposing, scarlet fever in 11 diarrhea in 3, pneumonia in 2 measles in 2 vaccination, rheumatism cervical adenitis and septic infection each in 1 In 1912 McCrink[10] found 64 cases reported 17 following scarlet fever

By now the number could be greatly increased, as there are numerous case reports in the recent literature and still purpura fulminans remains an unusual form of purpura characterized by sudden onset short duration large areas of purpura often symmetrical in distribution, accompanied at times by hemorrhage from the mucous membranes and in various tissues such as the adrenals Its occurrence is most frequent in infants and children Blood findings vary but as a rule they are not very abnormal There may or may not be a platelet reduction

HEREDITARY AND FAMILIAL PURPURAS AND BLEEDINGS

Heredity with familial incidence of purpura and bleeding is found in patients with and without thrombocytopenia The former less frequent in occurrence than the latter already has been discussed under thrombocytopenic purpura In patients with hereditary and familial occurrence purpura on the whole is less prominent than the bleeding tendency with bleedings from various tissues and organs of the body

Hemophilia

Frequent in its occurrence and for a long time of great interest to both historians and physicians is hemophilia This has very definite characteristics rendering its recognition easy and definite In its characteristics in many ways it is the antithesis of thrombocytopenic purpura It has prolonged coagulation time normal platelet count normal bleeding time negative tourniquet test and eventually, normal clot retraction Its hereditary transmission is characteristic in that it occurs in the males and is transmitted through the females Bleeding in hemophilia usually follows trauma It is believed to be due to deficiency of anti hemophilic globulin Another view is that it is due to a circulating anticoagulant anticephalin True purpuric skin lesions are infrequent although ecchymoses in the skin often follow slight traumas Hemarthrosis is frequent Hemophilia is discussed in detail in Chapter XX of Oxford Medicine which follows this chapter

Pseudohemophilia Thrombasthenia

Under this heading can be placed patients in many of whom there are similarities to or features identical with patients having hemophilia except for the lack of regular transmission through females to males i e they lack the characteristic heredity of hemophilia In some families the clotting mechanism with attendant changes is exactly that of hemophilia while in many others as will be seen subsequently there are variations from these characteristics leading various observers to have given them different names

Heredity and Clinical Features

As already discussed under the heading thrombocytopenic purpura familial and hereditary tendencies appear in purpura patients Some of the patients show thrombocytopenia and the others features of the blood typical of thrombocytopenic purpura (purpura hemorrhagica), others have no decreased platelet count but may or may not show such features as prolonged bleeding time, prolonged coagulation time non retractility of blood clot, these being found in varying combinations Glanzmann has suggested the term, *hereditary hemorragic thrombasthenia*, describing 8 families containing from 2 to many bleeders in several generations with the tendency transmitted by both sexes but usually through the females The cases were characterized clinically by bleeding from mucous membranes, from cuts and abrasions, operative wounds and after dental extractions but without purpura and with little tendency to intracutaneous bleeding Platelets were normal or insignificantly decreased The blood might show the changes of secondary anemia Coagulation time was normal, although the clot was soft and in some patients did not retract Bleeding time was normal Except for two partially confirmatory reports, those of Kromecke[13] and van der Zande[154], no other similar cases have been reported, suggesting either excessive rarity or faulty observations Glanzmann's[5] conception of thrombasthenia as a functional deficiency of the platelets has persisted and still is a matter of controversy

Von Willebrand[15] has reported a series of patients in clinical features and familial occurrence resembling those of Glanzmann These occurred in three families of Swedish descent which have lived for a thousand years in isolated communities in Finland, where considerable inbreeding and but little admixture with outside populations took place Von Willebrand obtained records of 124 members of these families of which 48 gave a history of bleeding, 17 were males and 31 females 10 of the females died from hemorrhage Von Willebrand was able to study a number of these individuals, 13 of them on some occasion showed the following features a normal coagulation time, a normal or high platelet count, normal clot retraction but a prolonged bleeding time and in the more sever cases, a positive tourniquet test The bleeding time was not uniformly or invariably prolonged sometimes it varied on different occasions in the same patient but tended to parallel severity of symptoms Von Willebrand attributed the bleeding to a functional abnormality of the platelets "thrombopathie", but recog-

nized a vascular component. He used the term *hereditary pseudohemophilia*, for them.

Handley and Nusbrecker[14] have reported a family in which there were 20 bleeders, 16 men and 4 women, among 85 individuals in 6 generations as shown in the chart (Fig 1). They studied in detail three members of this family, 1 male in the sixth generation and 2 females in the fifth. In these clotting time varied from normal to delayed up to 2 to 4 times normal; usually it was delayed, while bleeding time was normal, as were platelet counts.

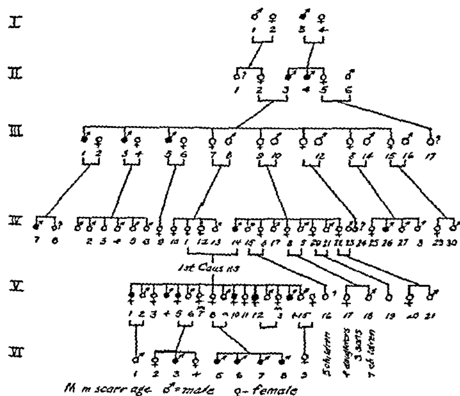


Fig 1 Family (reported by Handley and Nussbrecker[15]) with pseudohemophilia showing incidence of bleeding in 6 generations. The usual notation for males and females is used; the solid black dots represent individuals with history of bleeding.

A similar family (see Fig 2) has been studied by Levy[1] in which of 62 members in 5 generations 12 males and 8 females were affected All had bled frequently following minor degrees of trauma, 15 had had frequent epistaxis Four of the 8 females had excessive menstrual bleeding, and [illegible] had post-partal hemorrhages Prolonged bleeding followed tooth extraction in 4 cases, 2 had bleeding from appendectomy incision, and 1 had repeated hemorrhages after tonsillectomy 3 had gastrointestinal bleeding, pulmonary hemorrhages occurred in 4 1 had hematuria No petecchiae occurred in any of the 4 cases and the spleen was not palpable in them Both sexes may have the bleeding and either may transmit the tendency to bleed Coagulation time clot retraction, prothrombin time platelet count and capillary resistance were within normal limits Bleeding time varied from time to time in the same individual often it was prolonged especially when bleedings were happening Bone marrow studied in 1 case, was normal Five members of this family are known to have bled to death, 3 of pulmonary hemorrhage 1 from uterine bleeding and 1 from gun shot wound

Madison and Quick[18] reported a case similar to Levy s and Evans and MacLaren[19] have investigated a family with similar hereditary bleeding tendency and normal blood findings Geiger and Evans[illegible]

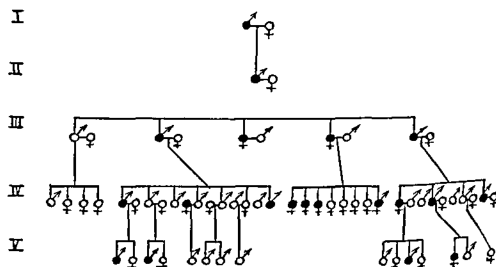


Fig 2 Family (reported by Levy[17]) with pseudohemophilia showing incidence of bleeding in 5 generations The usual notation for males and females is used the solid black dots represent individuals with history of bleeding

report severe gastrointestinal hemorrhage in a man and of his children in a family of 9 of whom 5 were bleeders Bailey and McAlpin' report 2 negro boys brothers with bleeding time usually prolonged platelet counts normal except once clot retraction normal in one and delayed in one clotting time normal and tourniquet test negative

Halliwell and Brigham report the occurrence of 5 male bleeders in three generations of a family bleeding time was prolonged in 4 of these bleeders but was variable at times greatly prolonged at others only slightly prolonged or normal coagulation time clot retraction prothrombin activity platelet count and tourniquet test were not abnormal Estern Medal and Dameshek reported 11 cases which were typical except that in only 5 cases was a family history of bleeding obtained

As will be seen from the preceding brief discussion of reports here is a group of patients with clinical features very similar and on the whole much like those found in hemophilia Clotting mechanism and character of transmission (heredity) differ from that of hemophilia Clotting mechanism varies considerably from group to group but usually is unlike that found in hemophilia It seems best to group these families under one heading For them the term *pseudohemophilia* generally has been used and although not thoroughly satisfactory appears to be the preferable term An excellent discussion will be found in an editorial[186] in Annals of Int Medicine for March 1947 The term *thrombasthenia* is preferred by some

Reference already has been made to the cases of Minot[9] and Buckman[96] the former with prolonged bleeding time and the latter with both prolonged bleeding and coagulation time but otherwise with normal blood findings Griffin[161] has reported . cases of this type One was a woman of 33 with epistaxis and other purpuric manifestations occurring in 4 generations and a girl of 9 without family history who had severe bleeding from nose and gums and subsequently profuse menorrhagia (Kennedy[1]) In the former bleeding time was prolonged while platelets and coagulation time were normal in the latter platelets were normal in number, bleeding time was prolonged and the clot did not retract

Little and Ayres[163] have traced a family of similar type through 5 generations having studied . patients with prolonged bleeding time normal coagulation time normal number of platelets and splenomegaly Rosenthal[161] mentions 2 cases a mother and a son of this type Rothman and Nixon[169] describe a boy of 13 observed for nine years whose

mother and brother bruised or bled easily, who bled unduly from slight traumata and had extremely severe nose bleeds, an hemorrhagic rash with measles *ecchymotic area in the skin and oozing after extraction* of a tooth Bleeding time was prolonged, coagulation time normal clot retraction was defective, platelets were not decreased in number

Bleeding commonly starts in early life sometimes in infancy and is often troublesome in small children whose tumbles and minor traumata frequently result in extensive ecchymoses and persistent oozing from superficial abrasions It may persist throughout life but in many cases it has become less troublesome after adolescence, particularly the tendency to epistaxis

Bleeding from the mucous membranes persistent and often profuse is a common and highly characteristic feature Epistaxis is very common as well as bleeding from the gums and from the uterus Bleeding occurs less frequently from the gastrointestinal tract and only occasionally from the kidneys or lungs Persistent oozing from superficial cuts and abrasions is common and resembles that in hemophilia Bleeding often occurs from operative incisions is extremely troublesome and may be fatal These patients are poor 'surgical risks" and unessential operations and particularly splenectomy should be avoided They may be even worse risks than cases of hemophilia or thrombocytopenic purpura, since transfusions or injections of antihemophilic globulin in hemophilia usually will stop bleeding temporarily in them whereas in this disease they have relatively little or no effect upon the bleeding Troublesome bleeding is common after dental extractions and may *occur in children after loss of deciduous teeth*

Bleeding into the skin is common in the form of ecchymoses, usually following trauma but is less conspicuous than in thrombocytopenic purpura and typical petechiae are much less common Bleeding into the joints has occurred in several cases but is relatively uncommon in contrast to hemophilia Intracranial and retinal hemorrhages have been recorded but are very rare

The tendency to bleed varies markedly in different individuals and in the same individual at different times The tendency does not necessarily parallel the length of the bleeding time or the result of the tourniquet test, although there is a general tendency to do so Precise figures as to mortality are not available As in hemophilia there is a high probability of recovery from any one individual attack of bleeding, but the accumulated mortality is substantial Of the 6 collected

cases reported by Estren and associates[221], which had been adequately studied only 2 died of hemorrhage. This is undoubtedly an underestimate of the ultimate mortality. Geiger and Evans[8] reported 17 fatalities among 97 bleeders collected largely from previous reports. As adequate blood studies had been made in only one of these fatal cases, it is possible that in some the bleeding may have been due to *some other cause. However, as other bleeders in the same families* showed typical manifestations of the disease, there is a strong presumption that most of them died as a result of it. Geiger and Evans[8] figures may underestimate the ultimate mortality, as many of the survivors were not followed throughout their life span. All but one of the fatal cases were in women. This greater mortality is not due primarily to the additional risk from uterine bleeding, as there was a greater general tendency to bleed in most of these cases. The reason for this sex difference is not known.

Pathological Physiology

The pathogenesis of the bleeding is undetermined. Attempts to demonstrate a functional defect of the platelets have been mentioned and evidence for this in some patients is quite convincing[301]. This was demonstrated by observations of Alexander and Landwehr[301] on a patient with purpura, prolonged bleeding time, increased capillary fragility, poor clot retraction, normal platelet count and normal clotting time. This patient showed a coagulation defect indistinguishable from that observed in thrombocytopenic purpura, reflected in an elevated recalcification time and high residual serum *prothrombin* activity. This condition could be rectified by the addition of normal platelets to the patient's deplateletized plasma, whereas the patient's platelets were unable to correct the coagulation defect induced in normal plasma by deprivation of its platelets. In this patient the platelet count, at first normal, dropped later to thrombocytopenic levels. This suggests a possible relation between thrombasthenia and idiopathic thrombocytopenic purpura.

Pseudohemophilia probably is not due to a dysfunction of the spleen. In most cases the organ has not been enlarged or at least not palpable. In the few cases in which splenectomy has been carried out there has been little if any effect on the bleeding. At best it is in no way comparable with that often seen following splenectomy in thrombocytopenic purpura.

Macfarlane has emphasized the importance of the role played by the minute vessels in hemostasis Normally trauma to these vessels is followed quickly by a constriction, which mechanically checks oozing until sufficient time has elapsed to permit agglutination of platelets and the formation of a firm clot, which will occlude them In certain pathological states including this syndrome and thrombocytopenic purpura, these vessels appear to be abnormal, they fail to undergo constriction after injury and permit continuous oozing which prevents the formation of an occluding clot or thrombus He reports that the capillary loops in the nail beds in these diseases are distended and tortuous When a single capillary loop in a normal individual is punctured with a fine glass fiber after a slight hemorrhage it quickly contracts and disappears and remains invisible for from 20 minutes to 2 hours In these diseases there was no constriction after puncture and bleeding into the tissues persisted

These observations of abnormal appearing capillary loops, which fail to constrict and which bleed progressively after injury, have been confirmed Perkins [2] has reported similar findings in 1 case and Levy in 3 cases of this syndrome It seems possible, therefore, that vascular abnormalities plan an important and perhaps a major role in the bleeding tendency, although the tourniquet test is not so uniformly and strongly positive as might be expected, if this was the case The existence of some associated defect of coagulation possibly due to an abnormality of the platelets, has not been excluded

Treatment

Treatment has been unsatisfactory Superficial bleeding usually can be controlled by local applications of fibrin foam and thrombin solution under moderate pressure Internal hemorrhages however have been relatively uninfluenced by transfusions and other customary procedures, although they counteract the effects of acute blood loss There are spontaneous variations in the tendency to bleed however and in a majority of the cases bleeding eventually ceases before exsanguination occurs

Recurrent Hemorrhage

Closely allied to purpura although not strictly speaking a form of purpura is a condition in a group of patients in whom recurrent hem

orrhages occur Among these epistaxis is a particularly frequent form although hemorrhage may occur from various other parts of the body both from cutaneous surfaces and various mucous membranes Very often but not always this condition appears in several members of the same family and in succeeding generations so that in these there is a definite hereditary or familial tendency to be made out As so often it is hereditary or familial it has been classified among these and described here

The condition apart from being annoying by reason of repetition of occurrence may be serious as a cause of severe anemia or even be fatal from blood loss in some families there having been a succession of deaths as a result of continued hemorrhage of this nature Both sexes are involved and there is no limitation of transmission by either sex as is true of hemophilia in which transmission is through the female with occurrence of bleeding only in the male

In some the hemorrhage occurs from telangiectases (spider angiomata) and to this group with a history of heredity the names Rendu[16]-Osler[168]-Weber[169] disease and also hereditary hemorrhagic telangiectasia (Hanes[170]) and heredofamilial angiomatosis with recurring hemorrhages (Goldstein[171]) have been given in other of these bleeders no telangiectasis can be made out Genuine purpuric lesions may occur in some of these patients but this is exceptional As a rule no abnormality can be made out in the blood other than the picture of secondary anemia following more prolonged bleedings Sometimes however changes do occcur in the constituents of the blood concerned in clotting

This condition for convenience will be discussed under the descriptive terms non familial recurrent epistaxis familial recurrent epistaxis without telangiectasia familial recurrent epistaxis with telangiectasia and familial recurrent hemorrhage other than epistaxis with and without telangiectasia

Non familial Recurrent Epistaxis

Numerous cases of this type have been reported especially those with telangiectases (Steiner[172] and Goldstein[171] in their papers cite such cases giving bibliographic references) Those with telangiectasia (spider angiomata of the mucous membrane) very probably bleed merely from trauma to the superficial dilated blood vessels of the angioma Those without telangiectasia have no obvious cause for the bleeding Griffin[1?]

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These observations of abnormal appearing capillary loops which fail to constrict and which bleed progressively after injury, have been confirmed Perkins has reported *similar findings in* 1 case and Levy[137] in 3 cases of this syndrome It seems possible, therefore that vascular abnormalities plan an important and perhaps a major role in the bleeding tendency, although the tourniquet test is not so uniformly and strongly positive as might be expected if this was the case The existence of some associated defect of coagulation possibly due to an abnormality of the platelets, has not been excluded

Treatment

Treatment has been unsatisfactory Superficial bleeding usually can be controlled by local applications of fibrin foam and thrombin solution under moderate pressure Internal hemorrhages, however have been relatively uninfluenced by transfusions and other customary procedures although they counteract the effects of acute blood loss There are spontaneous variations in the tendency to bleed however, and in a majority of the cases bleeding eventually ceases before exsanguination occurs

Recurrent Hemorrhage

Closely allied to purpura although not strictly speaking a form of purpura is a condition in a group of patients in whom recurrent hem

great uncles 1 paternal aunt, 2 paternal uncles the father and 2 half sisters had had epistaxes A man of 28 was much the same as the previous case except the tourniquet test was negative a maternal uncle the mother and a brother had had epistaxes

As will be seen from these patients both men and women bleed and heredity is both paternal and maternal In all the platelet count was somewhat reduced but was not low enough to explain the nose bleeds

Familial Recurrent Epistaxis with Telangiectasia

There is a very extensive bibliography on familial epistaxis with telangiectasis (Rendu[167] Osler[168]-Weber[16] syndrome hereditary hemorrhagic telangiectasia (Hanes[1 9]) or heredofamilial angiomatosis (Goldstein[171]) and numerous families now have been recorded Rendu[16] perhaps deserves credit for first in 1896 associating epistaxis and multiple telangiectases as clinical manifestations of a distinct morbid entity although Legg[178] in 1876 described a family in which telangiectases occurred and Babbington's[174] family reported in 1865 may have had telangiectases as a cause of the nose bleeds although none were described Osler's reports[1,8], 1901 and 1907 stimulated much interest in the subject and have been followed by other reports with an increasing number of recorded families In 1917 Steiner[17] collected [illegible]5 families from the literature and added 3 of his own in 1931 Goldstein[171] in a paper entitled heredofamilial angiomatosis with recurring familial hemorrhages states there are on record in the entire available medical literature of the world about 90 or 95 families and about 500 or 550 persons afflicted with this condition in 1932 Hurst and associates[179] criticise Goldstein's paper as including other unrelated conditions but collect 49 families showing hereditary telangiectasis with hemorrhagic tendency to which they add 7 families making a total of 56 families Garland and Anning in two papers refer to 267 families with hereditary hemorrhagic telangiectasia usually with epistaxis[18] Obviously the condition is not a very infrequent one Apparently only one case has been reported in the negro[32] in which the familial incidence is far from certain

The local lesions have been described very well by Steiner[1] as follows The telangiectases seen in this condition are of three varieties the pinpoint which is most apt to be seen on the skin of the hands and face and which may be readily overlooked the spider form which is the most common and which Parkes Weber prefers to call spider

has reported 2 cases of the latter type In both the platelet count was definitely low, the bleeding time somewhat prolonged and coagulation time normal In one the calcium time was estimated and found to be normal, in the other prothrombin time was found normal No lesion of the mucous membrane of the nose could be found to explain the bleeding Griffin[173] believes that they show the characteristics of mild hemorrhagic purpura Such epistaxis in childhood probably is fairly common

As recurrent epistaxis sometimes is associated with such conditions as rheumatic fever, typhoid, etc, care must be taken not to overlook in those prone to nose bleeds the presence of systemic conditions of which the nose bleed is only one manifestation

Familial Recurrent Epistaxis without Telangiectasia

In 1865 Babbington[174] reported a family in which recurrent epistaxis occurred in 5 generations, no mention of telangiectases was made in his very brief report Lane[175] in 1917 reported 13 members in 3 generations that had experienced epistaxis during adolescence, presumably without telangiectases Goldstein[176] (1922) reported a family with recurrent epistaxis, again presumably without telangiectasia Blumenfeld[177] (1926) described familial epistaxis definitely without telangiectasis a man of 45 had recurrent epistaxis from childhood, he had severe anemia, platelets 104 000, bleeding and coagulation time normal Two brothers, 2 sisters and 4 of his children had recurrent epistaxis

Griffin[173] (1927) reported 4 cases of familial epistaxis without telangiectasis describing them briefly as follows A woman of 31 had had very frequent epistaxis and menstruation was somewhat prolonged she had slight secondary anemia platelets were 100,000 to 150,000, coagulation bleeding, calcium and prothrombin time were normal clot retraction was good the tourniquet test was slightly positive, there were no telangiectases in the nose the paternal grandmother, the father sister and 2 brothers had had epistaxes A man of 26 had had frequent epistaxis since childhood his blood showed no anemia, but the other findings closely approximated those of the first patient except the tourniquet test was negative, the mother, the mother's brother, 2 brothers and 3 sisters had frequent epistaxes A man of 36 was much the same except for being markedly anemic and having 76,000 to 126 000 platelets and a slightly positive tourniquet test a paternal grandmother - paternal

orange yellow tinge On it are numerous irregularly distributed cherry red areas averaging about 2 mm in diameter the border of many of which is formed by a close network of serpentine lines On pressure the color disappears for an instant These are most numerous in the

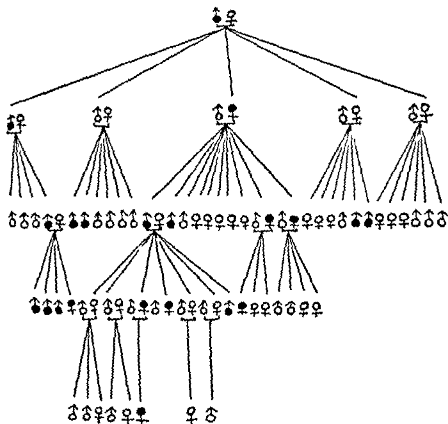


Fig 3 Family (family I reported by Steiner[101]) with 21 individuals in four generations having recurrent epistaxis with telangiectasia. The usual notation for males and females is used the solid black dots represent individuals with history of bleeding

region about the mouth and nostrils particularly the cheeks and on and just below the lip (This facial distribution of telangiectases strikingly resembles that in one of Osler's patients of whom a colored drawing is reproduced in Osler's paper in the Quarterly Journal of

angiomas rather than spider nevi, and the nodular type which may originate in the center of a spider angioma and finally form a solid vascular tumor, split pea in size They are most frequently seen on the nasal and buccal mucous membranes and on the mucocutaneous junction of the lips but may be found in the other locations mentioned above They begin as capillary dilatations and are bright red in color Later the venules give the cutaneous telangiectases a violaceous or purple color by participating in their formation The spots on the mucous membranes, however, always remain a bright red They may be seen early in life for Hanes has observed them in a boy of 8 years, but generally, if present at such an age they are not especially numerous for they do not attain their full number until after the age of 35 Even then they appear and disappear with marked frequency and seem to bear some relation to the bleeding being less marked if a considerable respite from hemorrhages is observed Parkes Weber speaks of a vicious circle being established by the repeated attacks of bleeding giving rise to a grave condition of anemia, which in its turn increases the tendency to hemorrhage

In these families there is no sex dominance, and transmission of the characteristic is through both sexes as in familial epistaxis without telangiectasis (Fig 3) There is no demonstrable abnormality of the blood in this condition other than the anemia that follows hemorrhage The anemia resulting from these hemorrhages especially those recurring frequently, may be marked and require transfusion or other methods of treating secondary anemia after the hemorrhage has been stopped by local means Patients develop ingenious methods of stopping nose bleeds as did two brothers that I saw while an undergraduate student of medicine at Johns Hopkins under Osler They, though their angiomata were of a different nature having developed in the sequence of the jaundice of Hanot s cirrhosis of the liver learned to control their nose bleeds by the utilization of a rubber finger cot connected with a short rubber tube, with the former held in the mouth the latter could be inflated in the nose, thus applying pressure to the bleeding angioma A similar procedure was used by one of the patients reported by Hurst and associates[179] The condition occurs chiefly in adults and often in the later periods of life

An idea of the skin lesions will be obtained from the description of two cases seen in my clinic at the Peter Bent Brigham and published by H B Richardson[180] In a man of 58 the face is pale and has an

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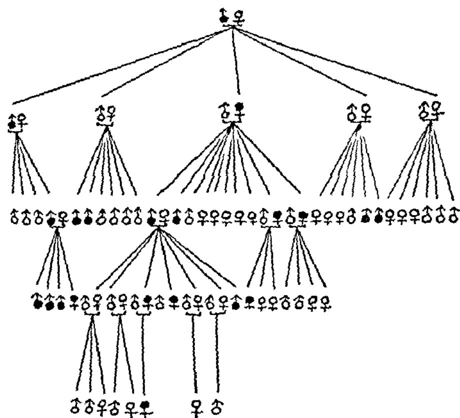


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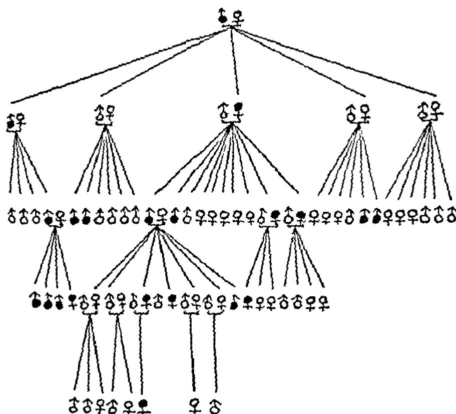


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Familial Recurrent Hemorrhage other than Epistaxis

Since the telangiectases may occur on either skin surfaces or mucous membranes it is not surprising that epistaxis is not the only form of hemorrhage that occurs Besides from the nose hemorrhage from such locations as conjunctiva ears cheeks lips various parts of the mucous membrane of the mouth and from the skin surface of different parts of the body have been described in some patients the hemorrhage now is from one place and now from another Since in all of these regions the telangiectases are readily visible diagnosis of the nature of the bleeding presents no difficulty

According to Moyer and Ackerman [5] hereditary telangiectases are characterized by disseminated abnormalities of capillaries small venules and small arterioles which have the appearance of hemangiomata or telangiectases or both They vary from typical spider nevi to pea size hemangiomata They occur most commonly on the skin and mucous membranes but may involve any organ The cutaneous or mucosal vascular lesions are composed of dilated small vessels which histologically comprise a single layer of endothelium underneath a much thinned layer of epithelium The absence of muscular and elastic layers of the vessel wall is conspicuous The vessels are fragile and rupture easily Thrombosis is quite frequent and possibly accounts for occasional disappearance of the lesions in certain areas With such structure obviously only slight trauma is needed to cause bleeding Bleeding may be prolonged because of the lack of the elements in the wall of blood vessels of these lesions which cause contraction and fixation of closing clots Also not infrequently in some patients the telangiectases show a marked photosensitivity[2,5]

Hemorrhage from internal organs takes place too in these patients with familial telangiectases and here the suggestive diagnostic points lie in the presence of telangiectases on visible surfaces and the history of familial occurrence of hemorrhages which render probable such an explanation of bleeding from a concealed surface Other more usual causes of bleeding must be excluded even when there are present the above suggestive evidences before a diagnosis of this type of hemorrhage from a concealed surface is justified

A number of cases of hemorrhage from telangiectasis of the mucous membrane of the gastrointestinal tract have been reported which are to be grouped under this heading In many of these the diagnosis based on hematemesis or melena in a patient with multiple telangiectasis and

Medicine[168]) "There are many smaller areas above and close to the eyebrows There is a moderate yellowish pigmentation of the palate, on which a few red patches similar to those on his face are visible, as well as two or three on the buccal mucous membranes On the right side of the nasal septum, about 2 cm from the nares, is an area 5 to 10 mm long bright cherry red in color, consisting of three elongated *patches Beside this is a white area, suggestive of scar tissue In the* left nasal cavity are several small blood clots and on the septum there is a circle of red nodular elevations, with a shallow depression in the center Rhinoscopy, by Dr C B Walker, disclosed numerous lesions of this type on the septum and turbinates The trunk and lower extremities are clear, but on the dorsum of the right finger there is a red area about 1 5 mm in diameter, with sharply defined borders which disappears on pressure Under three of the nails are similar minute areas On the glans penis are two more but these cannot be pressed out

In his son of 25 on the left side of the nose, are two minute threadlike telangiectases of a radial arrangement On the cheeks, below the malar bones there is a slight telangiectatic enlargement of the finer vessels This is seen also in the ears especially in the fossa of the hilex and in both cases can be largely or entirely pressed out On the end of the tongue is a round pink, depressed area about 1 to 2 mm in diameter and not affectetd by pressure Rhinoscopy, by Dr C B Walker was negative, showing no telangiectases On the skin by the right little finger nail is a minute, cherry-red area and similar ones under the third and fourth finger nails of the left hand All these are blanched by pressure There is a minute angioma on the right upper arm No telangiectases are visible elsewhere The father for 10 years had been having severe nose bleeds the son had recurrent epistaxes as long as he can remember The family history is as follows, the mother of the first patient, his sister, a maternal cousin and her 2 sons and 2 *daughters*, and a son by his first wife (described above) have had recurrent epistaxes with spots on the face noted in a number of these "

FitzHugh[181] points out that in some of these patients both spleen and liver are enlarged and that they show an increasing intolerance to transfusion Treatment should consist in stopping the hemorrhage by local styptics, pressure or cauterization Radium should be effective in application to the telangiectases and carbon dioxide snow has been effective in their treatment when their location is suitable for its application

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a personal and familial history of epistaxis or other bleedings, has been presumptive, though probable, inasmuch as direct examination of the bleeding tissue was not made In some, however, at operation or autopsy the actual lesion has been demonstrated For example, Boston[18] reports one such patient with telangiectases on face scalp, chest and lip, in whom at operation for gastric hemorrhage the surgeon found two "naevus-like areas" in the stomach and another patient with skin telangiectasis who after death from severe gastric hemorrhage showed at autopsy small areas that might be regarded as of this nature In one of Osler's familial patients with telangiectasia of the skin[168] autopsy showed telangiectases of the stomach and Bennecke[183] describes an autopsy in which telangiectatic lesions were found on the lower lip and in the esophagus stomach, intestines and rectum McClure and Ellis[184] operated on a patient who for years had shown a large number of 'blood tumors of the skin", to find hemangiomata on the surface of liver and in the stomach, duodenum, jejunum and ileum The patient had no family history of a similar condition In 3 patients of hereditary telangiectasis with epistaxis reported by Hurst and his associates[1 9] besides lesions on the skin and mucous membranes of nose and mouth similar lesions were observed through the sigmoidoscope in the lower large bowel

These observations make it evident that telangiectasis may occur in any part of the gastrointestinal tract and be the cause of repeated hematemesis or melena Such an explanation should be considered whenever repeated bleedings occur and x ray examination shows no evidence of a local lesion such as ulcer or neoplasm, if there is a history of bleeding in others of the family and if skin or mucous membrane telangiectases are present the probability of this explanation is enhanced With rectal bleeding local inspection with proctoscope or sigmoidoscope may show a local telangiectasis and confirm the diagnosis

Repeated hemorrhage is reported too, from other structures *trachea bronchi* and *lungs*, and from the *genitourinary* tract, when no one of the usual causes of hemorrhage from these regions can be demonstrated When such bleedings are recurrent, and especially when there is a family history of bleeding the probability of local telangiectasis must be thought of as the cause If cutaneous telangiectases are found the probability of that cause is enhanced materially By bronchoscope the presence of tracheal or bronchial telangiectasis has been reported FitzHugh[181] has reported a patient with a history of personal and familial

bleedings and telangiectasis of the skin in whom the bronchoscope showed distinct telangiectases which bleed on the slightest pressure in the trachea and left bronchus Interestingly enough this same patient by proctoscopy showed that the entire mucosa of rectum as far up as the sacral promontory is speckled with lesions which look like tubercles but microscopically were numerous areas of telangiectasis

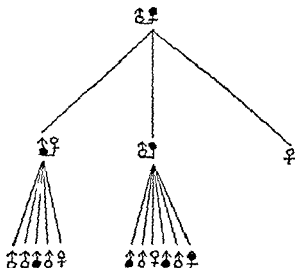


Fig 4 Family (reported by Libman and Ottenberg) with 7 individuals in three generations having recurrent hematuria The usual notation for males and females is used the solid black dots represent individuals with history of bleeding

Interesting is a rare combination of hemorrhagic telangiectases associated with pulmonary arterio venous fistula developing from angioma a condition not so rare when not associated with cutaneous telangiectasia These patients may show a typical triad of cyanosis polycythemia and clubbing of fingers and toes without as a rule cardiac enlargement They may or may not have hemoptyses Some of these patients have had successful removal of the pulmonary angiomatous lesion

Like the group of familial epistaxis without telangiectasis there may be recurrent *familial hemoptysis* without demonstrable telangiectasis Libman and Ottenberg[1] have reported under the title of hereditary

hemoptysis" such an occurrence in 7 members of one family (Fig 4) In none were skin telangiectasia observed, in 2 bronchoscopic examination was made but no telangiectases were seen in none was there evidence of pulmonary tuberculosis Bleeding in them began at about the age of puberty or in early adult life and recurred repeatedly through life It did not seriously impair health

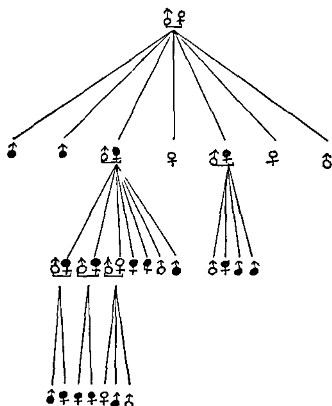


Fig 5 Family (reported by Guthrie[109] and further reported by Hurst[118]) with 16 individuals in three generation having familial recurrent hematuria The usual notation for males and females is used the solid black dots represent individuals with history of bleeding

Bleeding from the *kidney* of similar type has been reported Guthrie[186] as idiopathic or congenital hereditary and family *hematuria* reports 12 cases in one family, and later Hurst[187] with further observation of the same family finds that 16 individuals in 3 generations have shown the condition (Fig 5) and cites Attlee as having reported 3 similar cases

in another family In 1909 Aitken[188] reported 10 certain and 1 doubtful case in another family (Fig 6) No mention of telangiectasia in these families is made

In familial hematuria bleeding usually is noted very early in life and possibly exists from birth Usually very small amounts of blood are found in the urine sediment almost constantly from time to time there are attacks of hematuria when the urine is definitely bloody in the gross being bright red rather than smoky The attacks of hematuria have *no*

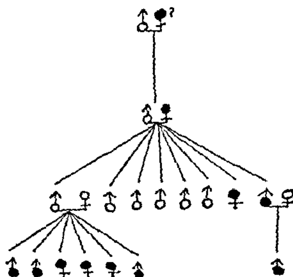


Fig 6 Family (reported by Aitken[113]) with 10 individuals and 1 doubtful case in three generations having recurrent hematuria The usual notation for males and females is used the solid black dots represent individuals with history of bleeding

regular intervals of occurrence and are associated with no particular time of day or kind of bodily activity Special sorts of food do not seem causative although this is not agreed to by all The paroxysmal hematuria persists for many years possibly through life with some tendency to decreasing frequency with advancing age Curiously enough it does not seem productive of more than very slight anemia The paroxysms of hematuria usually are associated with moderate systemic symptoms as slight fever malaise headache nausea vomiting

and slight pain in back or legs They often are attributed to catching cold, but it is not certain whether there is an antecedent respiratory infection, or whether this is merely a systemic effect of the attack of hematuria The attack usually begins abruptly, lasts a day or two, and then the hematuria gradually decreases over a period of a week or two It is definitely hematuria not hemoglobinuria Normally-appearing red cells and blood casts are nuemrous a few hyaline casts may be found albuminuria is present, sometimes more than seems proportionate to the amount of blood present These bleeders show no definite evidence that the condition is a nephritis although one or two in these reported families are said to have died from uremia, and Hurst[187] in a later study of the family reported by Guthrie[188] takes the view that it is a nephritis and he calls the condition, "hereditary familial congenital hemorrhagic nephritis" Unfortunately so far there is no recorded autopsy on one of these patients and no one knows just what the kidneys do show as cause of the bleeding

Conner and Bumpus[189] mention having observed 5 cases of recurring hematuria with a history of bleedings of some sort in other members of the family In these patients no positive proof of local telangiectasia is offered, and there were no pathological examinations of the kidneys to show the cause of the hematuria, but there are reported isolated cases where in kidneys removed on account of bleeding, localized telangiectases were found

Uterine and *bladder bleedings* of this same general nature may occur Reports of these however, so far as I have found, are not very satisfactory

In patients with familial recurrent bleedings with and without demonstrable telangiectases evidences of *cerebral hemorrhage*, such as hemiplegia occur Whether this results in these individuals from telangiectases within the central nervous system does not seem to have been placed on a surer foot of diagnosis than that of presumption from concomitant findings since I have found no record of anatomical demonstration in such cases of such a cause for intracranial hemorrage Angiomatous lesions do occur, however in the central nervous system Lindau[190] described a *symptom complex* (*Lindau's disease*) of angiomatous tumor in the retina and central nervous system of a heredofamilial character, and recent literature contains a number of case reports of Lindau's disease Intracranial hemorrhage does occur from angioma of cerebral tissues as in the case of Buckley[191], referred to by Cushing and

Bailey[19], and in the two cases reported by Ruhl[193] Cushing[194] describes 3 children with symptoms of cerebral hemorrhage and cutaneous nevi in 2 of whose brains angiomatous conditions were found Two showed nevus of the face and the third nevus of both face and arm Kufhs[19] has reported a case with heredofamilial multiple angiomata of the face and of the cerebral tissue and Jaffe[195] one with multiple hemangiomas of the skin cerebral tissues, thyroid, lungs, intestine and spleen So there seems no reason for not accepting these cerebral disturbances in patients with familial bleedings with or without cutaneous telangiectasis as resulting from intracranial bleeding of similar angiomas in the central nervous system

Treatment of Recurrent Hemorrhages

Treatment of these patients with recurrent hemorrhage should be directed first at stopping the local source of bleeding if that is possible This involves applying a vasoconstrictor or styptic to the bleeding point cauterizing it with nitrate of silver or the actual cautery or excising it or packing as in bleeding from nose or uterus Often the local lesion can not be reached although this is becoming increasingly possible by the use of various electrically lighted instruments such as the laryngoscope the bronchoscope the gastroscope the proctoscope and the cystoscope If local bleedings can not be treated directly, such measures as complete rest probably under strong sedation and a limited diet especially if the bleeding comes from the gastrointestinal tract should be carried out If anemia is acute and marked transfusions of blood should be given if less marked and chronic the anemia should be treated with iron and possibly folic acid If there is any defect in the clotting mechanism this should be treated by appropriate measures There is nothing known, which will decrease the tendency to recurrence of bleeding in these patients except guidance of the patient in guarding against local traumata which often are causative in starting bleeding

Hereditary Familial Purpura Simplex

Except for its hereditary and familial incidence these cases resemble those already described under the heading Purpura Simplex It is characterized by spontaneous ecchymoses mostly but not exclusively in

females occurring commonly at the climacteric Davis [1] has reported the condition in 27 families with 88 members, 84 of them females, having spontaneous ecchymoses In 9 of the 27 families purpura occurred in only 1 generation, in 12 in 2 generations, in 5 in generations and in 1 in 4 generations Of the 88 patients 79 had purpura simplex, 6 purpura of Schonlein-Henoch type, 2 bruised on trivial injury and 1, a boy, had pseudohemophilia

Platelet counts and bleeding and clotting times are normal in these patients, but the capillary resistance test often is positive Visceral hemorrhages do not occur Not infrequently this type of purpura is associated with rehumatic fever or rheumatoid arthritis Many of these individuals never seek medical advice and do not know that relatives are affected so it is difficult to develop a family history for one of them

FIBRINOPENIA

Another cause for bleeding is a deficiency in the circulating blood of fibrinogen This, judged by reported cases is not a frequent cause of hemorrhage Rabe and Salomon[19] have described a boy who bled profusely from cuts and who had marked bruises following slight trauma The only blood abnormality was absence of fibrinogen In this case there was no family history of bleeding Opitz and Frei [98] have described a similar case in a girl Nissen[200], Costex and associates [01], Heinild[202] Henderson and associates[203], Pinninger and Prunty [04] among other have discussed this condition and reported cases Congenital forms occur[201 202 03] and some claim that these are more frequent than the sporadic or acquired forms [06] Rocha e Silva and associates [05] demonstrated a great reduction in circulating fibrinogen in experimental shock produced by trypsin peptone and ascaris extracts

These patients usually have long periods of remission despite the fact that the fibrinogen remains absent from the blood Clinically there is a strong resemblance to hemophilia, although joint involvement is infrequent (Sturgis [49]) According to Quick diagnosis is simple in that the blood is absolutely and permanently incoagulable, the only other condition in which this is true being acute yellow atrophy of the liver The absence of fibrinogen from the blood can be demonstrated by the failure of saturating with sodium chloride or quarter saturating with ammonium sulfate to produce a precipitate Also heating the serum to 60°C will leave it clear, indicating the absence of fibrinogen (Sturgis [49])

Kammerer[199] has called this condition a form of *sporadic pseudo hemophilia* Also the terms *congenital afibrinogenemia* [3], *constitutional familial fibrinopenia* and *congenital fibrinopenia* are used

Transfusions of fresh whole blood would seem to the proper treatment if and when hemorrhage was marked

HYPOPROTHROMBINEMIA

Hypoprothrombinemia is a not very infrequent cause of bleeding in man particularly in patients with jaundice However lowered prothrombin levels are found frequently without the occurrence of bleeding Prothrombin decrease occurs in numerous conditions including especially the new born infant and diseases with defective intestinal absorption and/or decreased liver function Lowered blood prothrombin level is detectable by various technics as an increase in the prothrombin clotting time If prothrombin concentration is much decreased hemorrhages may occur this hemorrhagic tendency usually can be corrected by giving vitamin K since deficiency of vitamin K from its defective absorption from the intestinal tract or its deficient utilization in the synthesis of prothrombin by a much damaged liver is the chief cause of prothrombin deficiency [97 2 8] Vitamin K is so widely distributed in plants that its deficiency in the body only very rarely is due to a deficiency of vitamin K in the food intake

Hemorrhagic Disease of the New Born

Hemorrhagic disease of the new born [9 10] is the result of a very low prothrombin concentration in the circulating blood It is a self limited disease, occurring only in the new born characterized by spontaneous hemorrhages in any tissue of the body The coagulation time usually is prolonged the clot is retractile platelets are normal in number and bleeding time rarely is prolonged Untreated about half of the infants die When human blood is transfused prognosis is very greatly improved especially if this is done as soon as bleeding is in evidence or the prothrombin time is found much decreased Vitamin K as noted under treatment in paragraph at end of this section is curative unless giving it is greatly delayed in relation to the beginning of bleeding

However capillary fragility is another causative factor in hemor

rhage of the new born (Moloney [4]), and this may be the prime cause in certain infants in whom prothrombin level is not low enough to be causative of their bleeding

SECONDARY HYPOPROTHROMBINEMIA

Hypoprothrombinemia occurs in chronic jaundice of any cause in certain liver diseases as cirrhosis and hepatitis even without jaundice and in certain intestinal diseases such as sprue, chronic ulcerative colitis, chronic ileitis, chronic diarrheas, ileac stomata with profuse discharge, short-circuiting operations on the intestine, etc [11, 6] These are diseased conditions which occur with considerable frequency If the hypoprothrombinemia in them is fairly marked, bleedings in any part of the body, including purpura, are likely to occur Actually purpuric conditions from this cause alone do not occur with any considerable frequency When they do occur, vitamin K will stop bleeding in many of these patients

Hypoprothrombinemia may be a development in salicylate therapy Govan [1] has reported abnormal prolongation of prothrombin time in 6 of 24 children receiving salicylate with return to normal with continuation of the salicylate Owen and Bradford [13] found a fall in adults receiving daily 10 gm of salicylate intravenously, in 5 of 25 of these epistaxis or splinter hemorrhages of the finger nails occurred Clausen and Jager [14] correlated degree of hypoprothrombinemia with plasma level of salicylate Park and Engelberg [15] reported prolongation of prothrombin time following quinine therapy, but Quick [16] failed to confirm this Apparently purpura or other hemorrhagic manifestations do not follow salicylate-caused hypoprothrombinemia unless thrombocytopenia is produced Such cases have been reported by Stevens and Kaplan [4], Troll and Menten and Rappoport Nixon and Barker [6] Possibly salicylate may have been a causative factor in the case reported by Heindl Anderson and Friedlander [7], discussed in the next paragraph although the authors regarded it as a case of idiopathic hypoprothrombinemia without thrombocytopenia

Smith and associates [0] have shown that a nitrogen mustard will cause a coagulation defect apparently of similar mechanism to what has just been described, namely the appearance in the blood of an anticoagulant similar to heparin

The frequent use of dicumarol therapeutically has brought on in

creased frequency of hypoprothrombinemia of grade sufficient to cause hemorrhagic manifestations[6] These must be watched for and prevented by decreasing or stopping dicumarol dosage if occurring some form of vitamin K is to be used therapeutically along with transfusions of fresh whole blood Recently lyophilized plasma has been described as a successful therapeutic agent in such patients (Cosgriff and associates [8])

Idiopathic Prothrombinemia

Idiopathic prothrombinemia was first described by Rhoads and Fitzhugh [9] in 1941 Eight additional cases (Beard quoted by Quick [3] Giordano [30] Murphy and Clark [31] Heinild [7] cases Hauser [33] Austin and Quastler [34] and Quick [3]) have been collected by Heindl Anderson and Friedlander [7] to which they have added a tenth patient Of these 2 were fatal 7 chronic and 1 [7] fulminantly acute but not fatal all were males except one This last patient studied by Heindl Anderson and Friedlander [7] had ecchymoses on arms and legs extensive extravasations of blood in the tongue and neck bleeding from mouth gums and genitourinary gastrointestinal and pulmonary tracts This patient was treated successfully with large doses of menadione bisulfate (hyl inone) and transfusions of whole blood In some of these patients there was evidence of familial occurrence These reports justify including idiopathic hypoprothrombinemia as a variety of bleeding from hypoprothrombinemia

Treatment of Hypoprothrombinemia

Hypoprothrombinemia particularly if marked enough to result in bleedings should be treated with vitamin K For this the synthetic preparation menadione sulfite which is water soluble should be used it can be given either by mouth or parenterally in jaundiced patients bile salts should be given by mouth in addition to the menadione in a dose of 0 2 gm daily the menadione being given in doses of 1 to mgm daily either by mouth or intramuscularly Larger doses 3 to 5 mgm of menadione sulfite should be given to patients with evidences of severe liver damage Many advise giving 1 to 2 mgm of menadione sulfite by mouth to expectant mothers on each of 2 days before delivery and 1 mgm intramuscularly to the infant on birth as prophylactic

rhage of the new born (Moloney [4]), and this may be the prime cause in certain infants in whom prothrombin level is not low enough to be causative of their bleeding.

Secondary Hypoprothrombinemia

Hypoprothrombinemia occurs in chronic jaundice of any cause, in certain liver diseases as cirrhosis and hepatitis even without jaundice and in certain intestinal diseases such as sprue, chronic ulcerative colitis, chronic ileitis, chronic diarrheas, ileac stomata with profuse discharge, short-circuiting operations on the intestine, etc.[11, 6] These are diseased conditions which occur with considerable frequency. If the hypoprothrombinemia in them is fairly marked, bleedings in any part of the body including purpura, are likely to occur. Actually purpuric conditions from this cause alone do not occur with any considerable frequency. When they do occur, vitamin K will stop bleeding in many of these patients.

Hypoprothrombinemia may be a development in salicylate therapy. Govan[1] has reported abnormal prolongation of prothrombin time in 6 of 24 children receiving salicylate with return to normal with continuation of the salicylate. Owen and Bradford[13] found a fall in adults receiving daily 10 gm. of salicylate intravenously, in 5 of 25 of these epistaxis or splinter hemorrhages of the finger nails occurred. Clausen and Jager[14] correlated degree of hypoprothrombinemia with plasma level of salicylate. Park and Engelberg[15] reported prolongation of prothrombin time following quinine therapy, but Quick[16] failed to confirm this. Apparently purpura or other hemorrhagic manifestations do not follow salicylate caused hypoprothrombinemia unless thrombocytopenia is produced. Such cases have been reported by Stevens and Kaplan,[8] Troll and Menten and Rappoport, Nixon and Barker.[6] Possibly salicylate may have been a causative factor in the case reported by Heindl, Anderson and Friedlander, discussed in the next paragraph although the authors regarded it as a case of idiopathic hypoprothrombinemia without thrombocytopenia.

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leucemia and 2 with essential thrombocytopenic purpura intravenously with toluidine blue dissolved in 250 to 500 c c of normal saline solution giving from 1 to 4 mgm of toluidine blue per kilo of body weight This in each patient stopped generalized oozing of blood except from ulcerated areas but the effect did not persist This was a preliminary report 4 of the patients had purpura as part of an incurable disease leucemia in itself shortly fatal while a fifth with thrombopenic purpura died in a few days of intracranial hemorrhage A sixth of this group also having thrombocytopenic purpura continued to have petechiae periodically

Allen and his associates[44] also have treated effectively various other hemorrhagic conditions with toluidine blue and protamine sulfate Parkin and associates[1] found no effect on the hemorrhagic phenomena from protamin sulfate and toluidine blue given to a patient with thrombocytopenic purpura However Holoubek Hendrick and Hollis[81] *report dramatic results from toluidine blue in 2 patients after* giving intravenously in one 132 mgm followed next day by 68 mgm and in the other 3 mgm per kilo of body weight

The chief interest in this report lies in the new light thrown on the mechanism of bleeding in purpura adding to other demonstrated factors the very probable presence of hyperheparinemia The therapeutic agents described had only a temporary influence but possibly may prove to have some value in the treatment of purpura additional studies are needed in the way of exploration of this heparin relationship *and its possible better therapeutic control in the purpuras*

CIRCULATING NON-HEPARIN ANTICOAGULANTS

A hemorrhagic condition in man due to an anticoagulant in the blood occurs That this may be and probably is heparin or some substance closely related to heparin is discussed in the preceding section However there is evidence that this anticoagulant at times is other than heparin or a heparin like substance Lozner and associates[238] report an anticoagulant in the blood of a 61 year old mulatto with a hemorrhagic disorder which was relatively unstable and non dialyzable with an effect not altered by protamine and in these respects unlike heparin Lawrence and Johnson[239] and Munro[240 241 12] report an anticoagulant developing in the plasma of hemophiliacs following repeated transfusions which was associated with the gamma globulins Craddock and

procedures If hemorrhage appears in the infant, hemorrhagic disease of the new born intramuscular menadione 1 mgm should be given promptly and repeated daily so long as there is any evidence of bleeding

In all of these patients if bleeding is severe enough to cause anemia blood transfusions should be given in addition to other treatment

HYPERHEPARINEMIA

Allen and Jacobson[17] produced hemorrhage experimentally in dogs by irradiation In these dogs the presence of an anticoagulant could be demonstrated which was indistinguishable from heparin For the present at least this may be considered to be heparin and that when present in excess, it would be causative of bleeding inasmuch as it would retard formation of clot to stop hemorrhage This they considered to be one mechanism in the bleeding caused by irradiation Irradiation in man as well as in dogs has caused severe thrombocytopenia prolonged bleeding time and prolonged clotting time[17] a condition clinically similar to thrombocytopenia purpura whether essential or symptomatic In the dogs the bone marrow picture varies from one of hyperplasia to complete aplasia

In thrombocytopenic purpura cases Allen and his associates[18] by back titrations of their heparanized blood have shown that there probably is as compared with normals an increased amount of a heparin like substance *possibly heparin itself in the blood in other words* it is probable that in thrombocytopenic purpura there is hyperheparinemia to retard the stoppage of hemorrhages as one factor in their mechanism of bleeding one of the vascular vulnerability factors of the disease Parkin and associates[17] have not confirmed these findings

Allen and his associates[17, 18] have shown that protamin sulfate and toluidine blue can when injected intravenously stop the hemorrhagic tendency of irradiated dogs These are substances capable of binding heparin and rendering it biologically inactive so far as its anticoagulant properties are concerned These substances did not appear to affect any other phase of the clotting mechanism except to act as anticoagulants when present in excess they were effective even in the presence of marked thrombocytopenia but did not alter the platelet count in these irradiated animals Protamine sulfate and toluidine blue[18, 19] are of sufficiently slight toxicity to justify their use therapeutically in man

Allen and his associates[18] treated 6 patients 4 with acute or subacute

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Lawrence[13] were able to demonstrate in the sera of their patients precipitins against normal plasma and against Cohn's fraction I containing antihemophilic globulin, they believe the anticoagulant in these hemophiliacs is an antibody against the antihemophilic globulin Chargaff and West[14] report a woman with a hemophilia-like disorder in whom the prolonged clotting time was caused by a circulating anticoagulant not inhibited by protamine Fantl and Nance[1] have studied a 39 year old female with a bleeding tendency appearing several months after a normal pregnancy who had a circulating anticoagulant which appeared to be antithromboplastic for human brain thromboplastin but not for rabbit brain Conley and associates[16] have reported three patients one with hematuria and bleeding from a surgical wound in whom defective clotting was observed before any transfusions of blood, one with repeated hemoptyses with no x-ray evidence of lung lesion and one who was a hemophiliac who had had numerous blood transfusions The anticoagulants in these patients were not influenced by toluidine blue and protamine in a way to indicate a heparin nature They showed no proteolytic enzyme nor proteolytic enzyme inhibitor There was no increase in antithrombin activity in any of them In two of the patients response to thromboplastin appeared normal, in one there was some evidence of antithromboplastin The anticoagulant in these three patients seems to be of different natures but not heparin or a heparin like substance In these patients the anticoagulant seemed so potent as to be uninfluenced by massive transfusions no effective treatment could be advised by Conley and his associates[16]

The importance of these studies and those discussed in the previous section lies in the fact that in some patients with hemorrhagic manifestations the cause lies in the presence in the circulation of an anticoagulant, whatever its nature may be and not in each case of the same nature a mechanism differing from that in other of the purpuras and bleeders as discussed in this chapter

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CHAPTER XX

HEMOPHILIA

By RICHARD P STETSON AND EUGENE L LOZNER

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Synonyms — Hemorrhagic diathesis hæmorrhaphilia hæmorrhagophilia hæmorrhœa idiosyncrasia hæmorrhagica hematophilia hémophilie hémorrhagie constitutionelle morbus hæmaticus Bluterkrankheit Blutsucht amychemorrhagia

Definition — Hemophilia is an hereditary abnormality of the blood or blood forming organs exhibited only in males but transmitted through females characterized by a chronic liability to prolonged and immoderate hemorrhage which is dependent upon a delayed coagulation of the blood

HISTORY

In the Babylonian Talmud of the second century A D[1] it is stated that if two children of a mother or a child of each of two sisters die as a result of circumcision the third child need not be circumcised Maimonides[2] the famous physician and Talmudist of the twelfth century appar

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accept these as true manifestations of hemophilia for he asserted that males alone are affected and that transmission occurs through normal unaffected females This is referred to as Nasse's law in spite of its having been emphasized by Otto and other earlier writers on hemophilia The monographs of Grandidier (1855 2nd edition 1877)[7] and Legg (1872)[8] and the article by Immermann (1876)[9] are the most complete of the early subsequent accounts

In 1911 Bulloch and Fildes[3] published their exhaustive and critical analysis of 235 pedigrees of hemophilic families Of these pedigrees they admit only 44 as sufficiently authentic to permit of statistical study Krumbhaar's paper[10] on Otto gives an excellent historical review of the subject

Symptoms

The symptoms of hemophilia are dependent upon an impaired coagulability of the blood of the affected males resulting in a chronic liability to prolonged and severe hemorrhage which may be either internal or external

Severe and even fatal hemorrhage may occur from the umbilicus a few days after birth This is comparatively rare Of 98 cases reviewed by Birch[11] 29 had a history of bleeding during the first three weeks of life chiefly from circumcision stretching of the foreskin or from the umbilical cord In 77 of these 98 patients the first hemorrhage occurred within the first two years

In the case of a laceration there may be a fairly prompt diminution in the amount of bleeding but an oozing of blood persists in spite of the application of the usual pressure bandages Not uncommonly the initial bleeding will stop promptly only to be followed by a recurrence after a few hours or even days as the clot breaks away or is removed Bleeding may persist until an extreme degree of anemia or even death from exsanguination results Small puncture wounds are not as liable to be followed by excessive bleeding as are lacerations If the trauma is a blow which does not break the skin the bleeding may be subcutaneous to produce an abnormally large hematoma with an extensive area of swelling and discoloration The involvement of a joint results in an hemarthrosis with associated swelling pain and limitation of motion Spontaneous ecchymoses and petechial hemorrhages do occur rarely but when they constitute a prominent part of the clinical picture the diagnosis of a form of purpura must be considered

Whereas no part of the body is immune from bleeding there are

ently recognized the female transmission of the disorder in his decree that if two children of a mother die as a result of circumcision a third son whether he be of the first or second husband need not be circumcised This and other later dispensations make probable the recognition by the ancient Jews of hemophilia and some of its hereditary characteristics

Bulloch and Fildes[3] in their classical monograph on hemophilia attribute the first mention in medical literature of a disease resembling hemophilia to the Khalaf ibn Abbas called Albucasis the greatest surgical writer of the Moorish period (10th century) who tells of men in a certain village who when wounded or bled suffered an uncontrollable hemorrhage which caused death Boys of the same village bled excessively if their gums were rubbed harshly and they most commonly died Alexander Benedictus (1539) wrote of a frequently quoted but doubtful case that of a Venetian barber who died from accidentally cutting his nose with a pair of scissors Hoechstetter in 1674 tells of a boy who bled at birth from the umbilicus and subsequently experienced severe epistaxis, melena and frequent ecchymosis All of these symptoms disappeared before his eleventh year Banyer (1743) and Fordyce (1784) described cases of possible hemophilia In the Medecinische Ephemeriden published in 1793 an anonymous author thought to be G W Consbruch described the case of a boy of 11 years who bled to death from a slight cut on his thumb several brothers had similarly met their end while all the females in the family were free from this unhappy idiosyncrasy This is considered by Bulloch and Fildes as the first classical description of the disease in the history of hemophilia Alexander Rave in 1796 described hemorrhagic manifestations in himself and his three brothers

In 1803 Dr John C Otto[4] of Philadelphia published his epoch making contribution An account of an hemorrhagic disposition existing in certain families in which he described the occurrence of hemophilia in the male descendants of a woman named Smith from Plymouth N H With extreme clarity and perception Otto set forth the cardinal characteristics of hemophilia males only are affected and all are not liable to it Though females are free they are capable of transmitting it to their children The affected males are called bleeders for this is the name given to them This description marks the beginning of any widespread interest in hemophilia as a distinct morbid entity

In 1813 Hay[5] published the history of the noted Appleton Swain family of Ipswich Mass In 1820 Nasse[6] collected the then considerable data on hemophilia and added new material of his own Although he recorded the occurrence of bleeding in females apparently he did not

to account for the usually sudden and rapid swelling of the typical acute hemarthrosis Pain may be absent or mild in the smaller and more slowly developing hemarthrosis or may become excruciating as the tension in the joint capsule increases with continued effusion The joint at first fluctuant becomes tensely swollen and tender There is often moderate localized heat but no redness If there is any extra synovial bleeding bluish discolorations may appear near the joint in the course of a few days

In the milder hemarthroses motion is limited but slightly in the more severe instances the joint may be fixed in moderate flexion by muscle spasm A slight elevation of temperature is usual in large joint involvement and may reach 103° to 104° F in occasional instances A moderate leucocytosis is the rule

Roentgenograms during this stage show an increase in the size of the joint cavity and usually some soft tissue swelling with haziness about the joint cavity from the presence of blood in the tissues There are no bony changes unless these have resulted from previous episodes[13]

Resorption of the blood in the uncomplicated acute hemarthrosis usually is prompt and with proper conservative treatment the symptoms disappear within a few days Repeated hemarthroses of the same and various joints is the rule in the majority of hemophilics Gocht[14] has reported 45 hemorrhages into the right knee joint without the occurrence of permanent pathological changes

Chronic Hemophilic Arthritis

After one or many hemorrhages permanent changes in the various structures of the joint may take place to produce the stage of chronic arthritis This is defined by Key[1] as the stage in which the involved joint fails to return to an apparently normal condition after the hemorrhage In this stage after an acute hemarthrosis the joint may remain swollen tender and painful for an indefinite period There is permanent disturbance of function which increases with each recurrent acute attack The swelling in these acute attacks usually is less than in the uncomplicated acute hemarthrosis the blood is resorbed more slowly contracture deformity periarticular thickening and muscle atrophy are increasingly evident Bony ankylosis does not occur but fibrous ankylosis and muscle contractures may cause a flexion deformity which permits of practically no motion in the joint of the more extreme cases (Fig 1)

X ray examination of joints with chronic hemophilic arthritis reveals changes which vary with the nature and degree of structural damage

certain sites where hemorrhage is prone to occur Epistaxis is frequent in hemophilia as in other hemorrhagic diseases Spontaneous bleeding from the gums is not encountered as commonly in hemophilia as in certain other hemorrhagic conditions However, excessive bleeding from the gums during the eruption of the first and second dentition is of common occurrence Tooth extraction is a dangerous procedure in an hemophilic individual and has resulted in many alarming and even fatal hemorrhages A cut or bitten tongue may bleed for days Circumcision may reveal the first indication of hemophilia in a boy infant

Hematuria may be considerable and prolonged but is seldom in itself responsible for death Bleeding from the lower intestinal tract is encountered occasionally and severe bleeding may occur into the body cavities Gastric hemorrhage and hemoptysis are comparatively rare Weil[1] mentions a case of meningeal hemorrhage following lumbar puncture and reports having encountered four instances of hematoma of the orbit Hematomata in the central nervous system may cause transient or even permanent paresis and sensory changes

The natural course of the disease is one of varying severity and remission Hemorrhagic manifestations may be negligible for periods of weeks months or even years During these periods the blood coagulation time often shows wide fluctuations It may fall within normal limits although usually it is definitely abnormal and often is as prolonged as when bleeding occurs on the slightest provocation There is no marked correlation between the mildness or severity of symptoms and the length of the coagulation time

Acute phases of hemophilic activity attributable to no obvious precipitating cause may be mild or severe An acute infection in an hemophilic tends to result in a diminished coagulability of the blood with its attendant increased susceptibility to hemorrhage While there is no definite seasonal variation of symptoms patients in general are better during the summer than in the autumn winter and spring when upper respiratory and other infections are prevalent

Acute Hemarthroses

Among the most important and typical occurrences in hemophilia are hemorrhages into and around the joint cavities the acute hemarthrose which may be followed by chronic hemophilic arthritis The larger joints are involved most frequently but any joint may be affected The symptoms and appearance of the joint vary with the amount of intra articular hemorrhage Frequently there is no obtainable history of unusual trauma

luxation of the joint thickening of bone erosion of cortical bone due to subperiosteal hemorrhage notching of the joint surfaces and irregular erosions and exostoses of the joint margins ankylosis of tibia and femur ankylosis of patella and femur cysts in the bones sometimes communicating with the joint cavities at other times removed from the joint cavity calcification in subcutaneous tissues deposition of iron in subsynovial tissues calcification of subperiosteal hematoma flattening of head of femur deformities of head of humerus

Etiology (Heredity)

Whereas the fundamental cause of hemophilia is not known geneticists have established its inheritance as a sex linked Mendelian recessive characteristic which may be transmitted from affected males through their female progeny (Gates[16]) It is not transmitted through unaffected males (Table I)

Of 171 recorded instances of transmission analyzed by Bulloch and Fildes[3] 160 show transmission through the unaffected female 7 through the alleged affected male and 4 through unaffected males Those authors explain many of these apparent exceptions to the law of Nasse on the basis of intermarriage with an unrecognized female conductor and they do not feel justified in concluding that hemophilia can be propagated through the male Klug[17] in a study of 52 families descended from the Mampel bleeder family finds no instance of transmission by males

On the other hand the possible instances of propagation by the affected male cited by Bulloch and Fildes and the more recent pedigrees reported by Nissé[18] Mills[19] and Birch[11] offer substantial evidence that the condition is transmitted by hemophilic males to subsequent generations through their daughters Emphasis should be given to the statement of Macklin[0] that the only persons in an hemophilic family who can marry with impunity are the unaffected males and their de cendants All the daughters of an hemophilic male are potential carriers and may transmit the defect to half their sons

No instance of undoubted hemophilia in females has ever been reported although some questionable cases have been recorded Theoretically the mating of an hemophilic male with a female conductor might produce hemophilic daughters If such were actually the case it is remarkable that none have been found in any of the noted hemophilic families living in locations more or less geographically isolated where intermarriage is relatively common A probable explanation is that such a double quantity of defect results in a non viable embryo (Gates)

Key[15] describes the characteristic roentgenogram changes of a typical case of hemophilic arthritis as including "a markedly increased density of the synovial tissues and crater like depressions or punched out defects in the intra articular portions of the bone However many cases do not present these characteristic features and these cannot be diagnosed by



FIG 1 R W 35 year old American with repeated hemarthroses into elbows knees and ankles most severe of which was in right elbow at age of nine These have resulted in Volkmann s contracture of right forearm and hand flexion deformity of left elbow and right knee and talipes equinus of right foot

x ray alone Keefer and Meyers[13] reviewing observations by many authors list the following changes reported as occurring in hemophilic arthritis atrophy of bone irregular wavy notched double epiphyseal line narrowing or absence of the joint space curving of the diaphysis of the femur displacement of the median condyle of the femur sub

18 were doubtfully hemophilic and 127 were normal It is of interest that 79 of 130 daughters of transmitters in their turn transmitted the disease The marriage rate of male bleeders in bleeder families is very low as compared with similar rates in the females (9 6% to 36 8% Bulloch and Fildes) probably due to the fact that many hemophilics die before reaching a marriageable age

Although hemophilia is a predominantly inherited disease authentic cases where no heredity can be demonstrated have been reported the so called sporadic or de novo cases Their explanation is not completely apparent they may result either by the transmission of the disease through several generations of daughters[16] or by a spontaneous mutation of the chromosome involved[22]

The bulk of authentic cases of hemophilia have been reported from Germany Switzerland England and the United States Whereas it cannot be said that the condition is confined to the Teutonic race it does occur predominantly where marriage with people of this race has been probable

PATHOLOGY

There have been reported no consistently distinctive gross or microscopic abnormalities of the various organs endocrine glands or tissues in hemophilia at post mortem examination other than those produced in the joints injured by hemophilic arthritis

Joint Changes

The joint changes of hemophilia have been reviewed by Keefer and Meyers[13] The synovial membrane of an affected hemophilic joint is hypertrophied and the subsynovial tissues are thickened with fibrous tissue and contain large amounts of broken down iron containing blood pigment Early there are regressive changes in the articular cartilage with later necrosis and complete loss of it about the margins of the articular surface There may be irregular areas of cartilage destruction and around the edge of the destroyed area the cartilage may be heaped up with resultant changes similar to those occurring in hypertrophic (degenerative) arthritis The changes in the bone vary with the number and position of the previous hemorrhages If there has been subperiosteal hemorrhage erosion of the bone at that area may be evident with irregular new bone formation or irregular calcification of the hematoma Cysts in the bone are one of the outstanding features They may be in either

As early as 1849 Wachsmuth [1] noted the unusual fertility of women in bleeder families. In the series of 44 family pedigrees collected by Bulloch and Fildes[3] there was an average of 6.1 children per family. In this same group of 44 families there were 142 females who had children, and of

TABLE I

Parents		Offspring				
Mating	Chromosomes	Female			Male	
		Carrier	Normal	Hemophilic	Hemophilic	Normal
Male — normal	X	X x	X X		x	X
Female — carrier	X x					
Male — hemophilic	x	X x				X
Female — normal	X X					
Male — hemophilic	x	X x		x x	x	X
Female — carrier	X x					
Male — hemophilic	x			x x	x	
Female — hemophilic	x x					
Male — normal	X	X x			x	
Female — hemophilic	x x					

Table showing the inheritance of hemophilia, a recessive sex linked characteristic. A normal female possesses two sex chromosomes (X X) one derived from each parent. A normal male possesses only one (X) derived from the mother. x represents a sex chromosome carrying the hemophilic factor which does not manifest itself in the presence of the dominant X, a normal sex chromosome, but which produces a female carrier in this combination (X x). The existence of a female hemophilic (x x) is theoretical, as it is believed that this double quantity is lethal.

these 125 had sons. Of these 125 mothers 37 (29%) escaped having hemophilic sons, 39 (31%) had no normal sons, while the remaining 49 (40%) had both bleeders and non bleeders. In Birch's[11] more recent genealogical study 267 hemophilics had 122 normal brothers, thus approximately 70 per cent of the boys were hemophilic. 143 transmitters had 665 children, 385 of them were males and of these 240 were hemophilic.

18 were doubtfully hemophilic and 127 were normal It is of interest that 79 of 130 daughters of transmitters in their turn transmitted the disease The marriage rate of male bleeders in bleeder families is very low as compared with similar rates in the females (9 6% to 36 8% Bulloch and Fildes) probably due to the fact that many hemophilics die before reaching a marriageable age

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the intra-articular portion of the bone and communicate with the joint or at some distance from the joint line in the cancellous bone.

Blood Coagulation

Impaired coagulability of hemophilic blood has been recognized since the earliest accounts of the disease and constitutes one of its cardinal features. In 1893 Wright[23] devised a method for measuring the coagulation time of the blood and demonstrated that the coagulation time of hemophilic blood was greater than that of normal blood. He observed also a decrease in the coagulation time following severe hemorrhage.

The nature of the coagulation defect in hemophilia has been the subject of intensive investigation since first it was observed. Although much progress has been made towards its elucidation, the exact mechanism of the defect still is unsettled. An important reason for the widespread interest in the pathological physiology of this disorder perhaps is less its clinical importance than it is in the information which its understanding might yield to the solution of the problem of the mechanism of the coagulation of normal blood when it is shed.

The various theories of blood coagulation have been reviewed recently by Eagle.[24, 25] That most prevalently accepted is the so-called "classical" theory first formulated in detail by Schmidt,[26] namely, that a two-stage reaction takes place when blood is shed. At least four substances participate in the reaction: prothrombin (prothrombase, thrombogen, proserozyme), calcium, thromboplastin (thrombokinase, cytozyme, tissue fibrinogen) and fibrinogen. The first three of these are thought to react together in the first stage of the reaction to form thrombin, a material which then goes on in the second stage to change fibrinogen from its soluble form to its gel or insoluble form called fibrin. It should be borne in mind that with the possible exception of calcium and fibrinogen the chemical natures of the substances participating in this reaction are incompletely understood and in regard to prothrombin and thromboplastin at least are better considered physiological complexes than single chemical substances. It is generally conceded that prothrombin resides chiefly in the non-cellular plasma. The source of thromboplastin is a matter of greater controversy. In the "classical" theory it is described as originating in the cellular elements of the blood, chiefly the platelets, and in the tissues. Recently, however, Nolf[27] has pointed out that cell-free plasma can be shown to contain all the substances necessary for clotting and it is only the contact with a foreign substance that initiates the process. Thus it is apparent that in the plasma as well as in the platelets and in

the tissues there is a material which possesses thromboplastic or clot promoting activity That it is the same chemical substance that is involved in the reaction in each instance is not at all clear

A defect or deficiency in any one of these complexes necessary for the normal coagulation of blood might explain the abnormal coagulation in hemophilia The calcium and fibrinogen content of hemophilic blood have been shown repeatedly to be normal[28,29] Quick in 1935[30] clearly demonstrated that the prothrombin content of hemophilic blood was normal In 1916 Minot and Lee[31] observed that the transfusion of normal human citrated blood into a patient with hemophilia shortened his coagulation time toward normal limits More recently Govaerts and Gratia[32] and Patek and Stetson[33] observed that normal human citrated plasma which had been rendered cell free by passage through a Berkefeld filter also was capable of shortening the coagulation time of the blood of patients with hemophilia both in vitro and in vivo Subsequent investigations by Bendien and Van Creveld[34] and by workers at the Thorndike Memorial Laboratory[35,36,37,38] have shown that this clot promoting activity is associated with the globulin fraction of normal plasma The active principle of this globulin fraction is soluble in isotonic saline solution and is thermolabile The globulin fraction of hemophilic plasma possesses relatively little clot promoting activity Thus it appears that the blood plasma of the patient with hemophilia is deficient in one of the physiological complexes necessary for blood coagulation Lozner Kark and Taylor[39] have shown that this complex is independent of prothrombin and fibrinogen Howell[2] and others have chosen to call the deficiency one of plasma thromboplastin implying its similarity to the clot promoting material present in brain lung and other tissues

The above concept concerning the nature of the coagulation defect in hemophilia is not held universally Several observers[31,40,41] have presented evidence tending to show that the platelets of patients with hemophilia are less fragile than those of normal individuals Other observers[33,4] have disputed this and can demonstrate no difference Howell[2] has suggested that the source of the plasma thromboplastin may be the platelets The patient with hemophilia therefore may be both quantitatively and qualitatively deficient in this clot promoting factor a supposition as yet not definitely established

Blood Morphology and Chemistry

The platelets of hemophilic blood are normal in number and morphology The fibrinogen content of hemophilic blood is normal as are

the serum proteins[43] the total nitrogen chloride inorganic phosphorous blood cholesterol and hydrogen ion concentration[44] The chloride and bicarbonate distribution is normal[45] Stuber and Lang[46] have demonstrated a high fluoride content of the blood in hemophilia with a consequently slowed rate of glycolysis in the shed blood They attempt to explain the delayed coagulation on this basis Hoff and May[47] on the other hand found only minimal traces of fluoride in the blood of their case It is believed by Wright[23] that hemophilia results from calcium deficiency Hess[8] reported one case of hemophilia showing a negative calcium balance The importance of this is nullified by its occurring in a growing boy with icthyosis It has been shown experimentally that a level of calcium sufficiently low to interfere with blood clotting is far below the level compatible with life[48] Wright[3] and Sahli[9] reported bleeders who exhibited a neutrophilic leucopenia but these observations have not been confirmed generally and such a blood picture can not be considered typical in hemophilia Certainly a leucocytosis and an increase in the number of platelets is the rule after a hemorrhage in a patient with hemophilia as it is when blood loss occurs in a normal person Although the blood coagulation time is prolonged to varying lengths the character of the hemophilic clot when formed is normal[19] The reclotting phenomenon observed by Minot and Lee[31] is not peculiar to hemophilic blood but is observed in other conditions exhibiting impaired blood coagulability The bleeding time in hemophilia from a puncture of the skin is not longer than normal If there has been an appreciable chronic loss of blood the red blood corpuscles may be diminished in numbers and show the changes typical of hypochromic anemia

Diagnosis

The diagnosis of classical hemophilia ordinarily presents no difficulties if its possibility is considered A young male often with a slight degree of secondary anemia bleeding perhaps mildly but none the less persistently from any external or internal source always should suggest the diagnosis of hemophilia A past history of bleeding episodes from infancy usually following some minor trauma or a history of repeated attacks of painfully swollen joints with or without resultant deformity makes the diagnosis practically certain A family history of bleeding in the male collaterals should leave no reason to doub that the case is one of classical hemophilia A positive family history is not always obtainable or if obtained casually is subject to error and the possibility of sporadic or de novo cases must not be forgotten

Physical examination may or may not reveal pallor and the joint changes characteristic of hemophilic arthritis If the blood loss has been considerable and recent a moderate leucocytosis usually is present and if the hemorrhage is large and confined within the tissues or involves a joint the body temperature usually is elevated due to absorption of the products of blood disintegration

The exact diagnosis of hemophilia cannot be made without the demonstration of the characteristically prolonged coagulation time of the blood Of the procedures usually done in the diagnostic study of a patient exhibiting an hemorrhagic diathesis namely tourniquet test bleeding time coagulation time clot retraction and prothrombin time it is only the coagulation time which is abnormal in the patient with hemophilia However it is important to recognize that the coagulation time in hemophilia may approach or perhaps rarely reach normal after hemorrhage and between bleeding episodes

The test must be made with blood which is free from admixture of tissue juice for Howell[19] and others[30] have shown that the addition of such material to hemophilic blood in vitro markedly reduces the time required for the clot to form and may give completely erroneous results Methods of determining the coagulation time in which the blood is obtained by punctures through the skin capillary blood are not an accurate index of the blood coagulability due to the inevitable mixture of tissue juices and the consequently falsely shortened coagulation time

A modification[36] of the method of Lee and White[50] is a technique commonly used and satisfactory for determining the coagulation time of venous blood Five cubic centimeters of blood are drawn from an arm vein into a syringe rinsed previously with physiological salt solution The venepuncture must be performed skillfully and without probing and the flow of blood must be free and without bubbles of air entering the syringe After withdrawal from the vein the needle is removed from the syringe and two cubic centimeters of the blood are introduced gently and without bubbles into each of two 100×13 millimeter test tubes scrupulously clean and previously rinsed with physiological salt solution The tubes then are placed in a water bath or a beaker of water at a temperature of 37 Centigrade The first tube is observed from time to time by tilting it gently The end point is the time at which the surface of the blood *has jelled sufficiently to permit slowly inverting* the tube without loss of contents The second tube then is examined similarly If the discrepancy between the two tubes is no greater than five minutes the average time is used if the difference is greater than five minutes the longer time is used Normal blood tested by this method

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and Lee[31] Pickering[56] and Howell[illegible] have reported observations on males who exhibited a disorder apparently intermediate between hemophilia and purpura with alterations of both platelet counts and coagulation times

Symptomatic purpura dependent upon an underlying blood dyscrasia such as leukemia or aplastic anemia should be evident upon thorough blood examination Cirrhosis of the liver whether idiopathic or due to toxic poisons hemochromatosis and scurvy or overwhelming sepsis may give purpuric manifestations but should not be confused ordinarily with hemophilia after careful history taking and examination The same is true of allergic purpura with its normal blood platelets An acute rheumatic fever may be associated with epistaxis hematuria purpura and multiple but characteristically migrating joint involvement Epistaxis with or without hematuria may be the presenting symptom of a nephritis in which the coagulation time sometimes is slightly prolonged

Minot[57] has described a case of chronic dietary deficiency in a seventeen year old boy with repeated nose bleeds a history of bleeding for two days following tooth extraction and a slightly prolonged coagulation time His symptoms disappeared and his coagulation time returned to normal after correcting his dietary habits In the light of recent work on hypoprothrombinemiad consequent on dietary deficiency of vitamin K[53] it is possible that this and other similar cases may fall into such a category

Hemorrhagic disease of the newborn often is associated with a markedly delayed blood coagulation This condition appears only in the first week after birth is due to hypoprothrombinemia and responds to the administration of vitamin K[53]

Recurrent epistaxis hematuria hemoptysis and menorrhagia have been described as occurring in familial form Hereditary multiple telangiectasia may be diagnosed by the detection of the telangiectasia and otherwise normal findings on physical and laboratory examination For a discussion of these conditions and the various types of purpura see the chapter preceding this one (Chapter XIX Vol II)

The differential diagnosis of hemophilic joints is of extreme importance In the stage of acute hemarthrosis they must be differentiated from traumatic synovitis acute rheumatic fever acute pyogenic arthritis gonorrheal arthritis and osteomyelitis The sudden onset either spontaneously or after slight trauma the rapid progress and regression the lack of evidence of predominant local inflammation or general sepsis are characteristics of an hemarthrosis In the stage of chronic hemophilic arthritis differentiation must be made from tuberculosis syphilis and chronic arthritis of traumatic or unknown etiology In most of the cases

clots in from six to twelve minutes In patients with hemophilia the coagulation time may vary from twenty minutes to several hours

Quick[51] has reviewed those conditions which are associated with a prolonged coagulation time and must therefore be differentiated from hemophilia In brief they are fibrinopenia either congenital or acquired e g liver disease hypoprothrombinemia e g obstructive jaundice biliary fistula and certain intestinal disorders and the presence in the circulating blood of an anticoagulant This last condition is extremely rare[52] The two former conditions may be eliminated and differentiated by the performance of a chemical determination of the plasma fibrinogen and of a prothrombin time test

If for any reason the coagulation time cannot be determined it will be necessary to differentiate clinically hemophilia from the other important hemorrhagic diatheses Idiopathic thrombopenic purpura (purpura hemorrhagica) occurs in both males and females The coagulation time in this type of purpura usually is normal and the clot non retractile and friable There is an actual thrombopenia and the few remaining platelets vary greatly in size The bleeding time from a puncture in the skin is prolonged in purpura normal in hemophilia A tourniquet applied to an extremity produces multiple ecchymoses distal to the point of application in purpura more markedly than in most cases of hemophilia although a positive tourniquet test is seen occasionally in the latter condition Spontaneous ecchymoses purpuric skin blotches and petechial hemorrhages usually are prominent in purpura as is bleeding from the gums and mucous membranes Epistaxis is common to both hemophilia and purpura Joint involvement is exceedingly rare in purpura hemorrhagica but may be present in Schoenlein s purpura rheumatica in which condition the platelets are not reduced significantly

There is a form of purpura which is hereditary but which shows no sex linkage or other distinctive features of hemophilia and is characterized by a prolonged bleeding time Von Willebrand and Jürgens[53] have described the occurrence of such a form of hereditary purpura in a group of families in Finland

Abnormal bleeding of a purpuric type has been observed to occur in female members of some hemophilic families Hess[54] has described two families in which one member suffered from hemophilia and another from purpura More recently Wyllie and Ellis[55] have commented on the possible relationship between these two conditions and state that isolated features of purpura occur in certain hemophilics and vice versa It is probable that failure to distinguish between these diseases has been responsible for many of the reported cases of hemophilia in females Minot

are effective only in that the course of observation has kept the patient under careful supervision free from injury and has insured a good diet

General measures are of the utmost importance and should be directed towards the maintenance of good health adequate nutrition and protection against trauma

There is some evidence to suggest that the coagulation time of the blood is diminished after the ingestion of a meal rich in protein[61] but this is not a reason for giving to the hemophiliac an inadequate diet The value of a diet high in protein and adequate in minerals and vitamins in maintaining hemopoietic activity and general health is recognized If there is evidence of anemia from chronic blood loss the addition of optimal quantities of iron will enhance blood regeneration

A supervised regime is essential if undue trauma is to be avoided Rough play must be forbidden and the child should be taught the dangers of personal injury Oral hygiene and dental supervision is neglected by many hemophilics largely through fear of establishing a hemorrhage A soft brush or a pledget of cotton if the gums are spongy should be used carefully but consistently Cooperation between the dentist and the physician is essential

Infections are to be guarded against as any infection may precipitate an acute phase of the disease In this regard it may be said that vaccination venepuncture subcutaneous injections and intramuscular injections carefully executed may be done on hemophilics without danger The presence of adequate veins for transfusion is often of life saving importance to patients with hemophilia For this reason venepuncture should be done skillfully and veins never should be cut down upon except when absolutely unavoidable Any known hemophilic should be tested for sensitivity before serum of any kind other than human is administered as frequently they will have been sensitized for therapeutic purposes

Treatment of Hemorrhage

For controlling persistent internal hemorrhage or external bleeding which does not yield to ordinary local treatment there is nothing that offers more probability of success that the intravenous administration of a sufficient amount of whole or citrated human blood or plasma Transfusion is often a life saving measure and every hemophilic should have available a healthy donor of compatible blood group The beneficial effects of transfusion are evidenced by a diminution in bleeding and prompt reduction in the coagulation time There is usually a gradual return of

which have been operated upon the erroneous diagnosis of tuberculosis had been made The x ray findings are not necessarily characteristic and a careful history is of prime diagnostic importance

Prognosis

A patient with hemophilia lives in the constant shadow of the manifestations of the disease Many of the victims of the disease suffer severe *or fatal hemorrhage during the first year of life The entire duration of* childhood is hazardous The trauma from falls and injuries to which every active child is subject and the eruption of teeth often determine severe or fatal hemorrhage Carriere s statistics[60] in 1907 showed that 54 per cent of hemophilics died before the fifth year, 64 per cent before the tenth year and 89 per cent before the twentieth year These figures are entirely comparable to those of Birch[11] who states also that only 5 3 per cent of hemophilic babies can be expected to live beyond the fortieth year an expectancy one twelfth that of the normal baby With the passage of adolescence there is a tendency towards increased coagulability of the blood This together with the lessened exposure to trauma in the ordinary routine of adult life and a caution derived from experience combine for a happier outlook once maturity is reached

The probability of permanent damage to one or more joints with deformity and fibrous ankylosis is distressingly frequent and has been discussed

Treatment

The prevention of hemophilia is a matter of eugenics simple in theory impossible in practise Neither patients with hemophilia nor females of bleeder stock should beget children If however it is true that hemophilia may be produced also by spontaneous mutation of the chromosome this prophylaxis even if rigidly carried out could not be completely successful

General Measures

There is no specific treatment which has been proven to bring the coagulability of the blood to normal and keep it there In evaluating the benefits of any form of therapy the spontaneous remissions and exacerbations so characteristic of the disease must not be disregarded Many of the therapeutic measures which have been reported enthusiastically

Treatment of Joints

The acute hemarthroses should be treated by absolute rest in the most comfortable positions No tight constricting bandage should be used but an elastic supporting bandage may be comforting and enhance rest to the joint Cold compresses are of possible benefit For the relief of pain the usual oral analgesics and even opiates are indicated As the resorption of blood takes place guarded passive and active motion is to be attempted Physiotherapy in the form of radiant heat often is helpful during this stage and in the stage of chronic arthritis Moderate deformities which are not too severe a handicap to the patient are better left alone Severe deformities of the joints if treated at all must be treated conservatively by gentle physiotherapy traction pressure and supports Operative surgery usually is contraindicated

Other Therapeutic Measures

Various remedies have been suggested in the attempt to influence the course of hemophilia Eley Green and McKhann[64] have treated hemophilic children by the oral administration of an extract of human placenta Their results are encouraging but the effectiveness of their preparation has been variable and unpredictable in children and has not been beneficial to adults Superficial bleeding in hemophilia has been ameliorated by the production of an allergic reaction by intradermal injections of animal serum in previously sensitized individuals[6 66 67] In attempting control of hemorrhage from the larger blood vessels this procedure is ineffective Vitamins C K and P which have been shown to be concerned in the relief of certain hemorrhagic conditions are of no apparent value in the treatment of hemophilia The administration of calcium salts has no theoretical justification and is of no proved value[54]

The limitation of hemophilia to males raised the possibility of treating the disease by the administration of ovarian substance or various female sex hormones (Wright[68] Hynek[69] Birch[70] and others) The rationale of such therapy in hemophilia loses its theoretical appeal if we accept the genetic belief that a double quantity of the defect is lethal to the female embryo[16] In our experience with seven hemophilics[71] such therapy was of no value in controlling or preventing bleeding or in effecting any diminution in the coagulation time of either venous or capillary blood In these cases large amounts of material were given by mouth and parenterally over long periods of time Steinberg and Brown[72] have observed empirically that certain plant extracts apparently related to dicarboxylic

the clotting time to its pre transfusion level in the course of eighteen to seventy two hours[33] Satisfactory results have been observed after the administration of as little as 30 c c of citrated blood in general 100 c c transfusions are as effective as larger amounts unless the restoration of blood volume is a consideration Repeated transfusions frequently are necessary In preparation for any definitely indicated surgery a large transfusion should be given immediately before and during the operation Subsequent transfusions should be given as necessity develops probably at twelve hour intervals

The transfusion of normal Berkefeld filtered citrated human plasma is about as effective as is whole or citrated blood but its effect is some what shorter Plasma stored at ice box temperature for as long as two months has been used effectively to check hemorrhage[33] Unlike whole or citrated blood plasma need not be typed or cross matched before intravenous administration

The intramuscular injection of 10 c c to 50 c c of citrated blood or plasma usually is effective in reducing the coagulation time and in con trolling mild hemorrhage Blood for intramuscular injection need not be typed but almost invariably its use is associated with considerable local discomfort

The local application of some form of thromboplastic substance di rectly to a bleeding surface usually is helpful in staying hemorrhage from an exposed source These substances are more effective in dried form than in solution The direct application to the bleeding surface of a compress soaked with fresh normal human blood whole or citrated or in an emergency mashed up meat or any animal tissue may serve to arrest the bleeding A dried globulin substance derived from beef plasma has been used successfully as a local hemostatic in dental extractions and in lacerations[6] Russell s viper venom in solution has been used locally in hemophilia by Macfarlane with reported success[63]

The local application of styptics and calcium salts usually is unsatis factory One to ten per cent solutions of cocaine and a 1 to 1 000 solution of adrenalin chloride may be effective but unless the cessation of bleeding is prompt there is apt to be renewed bleeding of increased severity after the vasoconstricting effect has worn off

Some patients will react favorably to procedures that have failed to benefit others In the presence of obstinate bleeding any measure should be employed that offers a reasonable possibility of help and no probability of harm It is of the utmost importance however not to delay blood transfusion for the sake of trying any less sure procedure in the face of serious bleeding

Treatment of Joints

The acute hemarthroses should be treated by absolute rest in the most comfortable positions No tight constricting bandage should be used but an elastic supporting bandage may be comforting and enhance rest to the joint Cold compresses are of possible benefit For the relief of pain the usual oral analgesics and even opiates are indicated As the resorption of blood takes place guarded passive and active motion is to be attempted Physiotherapy in the form of radiant heat often is helpful during this stage and in the stage of chronic arthritis Moderate deformities which are not too severe a handicap to the patient are better left alone Severe deformities of the joints if treated at all must be treated conservatively by gentle physiotherapy traction pressure and supports Operative surgery usually is contraindicated

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acids accelerated the coagulation of blood following intravenous or intramuscular injection These substances are anticoagulant in vitro and it may be that their action is comparable to that of the intravenous injections of citrate solution[56] Two subsequent reports[73 74] have been encouraging However, definite evaluation must await further confirmation

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CHAPTER XXI

THE HEMOGLOBINURIAS

By G. M. MACKENZIE

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INTRODUCTION

All forms of hemoglobinuria must depend ultimately on a mechanism which injures the erythrocyte and thus destroys first its physiological and finally, its anatomical integrity: hemoglobin then escapes from the interior of the cell and diffuses into the surrounding medium. From that point on transport usually associated with hemoglobinemia and renal excretion of the blood pigments complete the sequence of events which culminate in hemoglobinuria. Just as there are many kinds of hemolysins so there are various ways in which they injure the erythrocyte.

The Normal Erythrocyte. The normal human erythrocyte is a biconcave disc consisting of a cell membrane or envelope enclosing hemoglobin salts, water (about 67 per cent) and many other substances in solution. The erythrocyte has a diameter of about 7.7μ and a thickness of about 1.95μ, its average volume is $90\mu^3$, its surface membrane contains about 80 per cent protein (stromatin) and about 20 per cent

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lipids (mainly lecithin and cholesterol) Normally the surface membrane is permeable to water and anions but not to salts as such nor to sodium and potassium, at least when the surrounding medium is normal plasma The discoidal form of the erythrocyte offers the advantages for oxygen exchange of a large surface at the expense of volume It is not correct to think of the erythrocyte as an inanimate bag filled with pigment, salts and water, it has a measurable metabolism similar to but less than, that of more highly organized cells

Mechanisms of Hemolysis Three Phases The pathological changes in the erythrocyte, which are caused by many, perhaps all hemolysins are characterized by three phases (1) *Injury to the cell membrane* resulting in alterations of the osmotic equilibrium of the interior of the cell and the medium in which it is suspended, the transfer of water anions and cations across the cell boundary is controlled by mechanisms which, even under normal conditions are imperfectly understood, what happens under pathological conditions, when a lytic agent acts on the erythrocyte, is even more obscure, but the result is an alteration of the permeability of the cell membrane An extensive literature has developed from studies designed to discover whether or not the erythrocyte is a "perfect osmometer" that is whether or not it obeys the laws of osmosis and diffusion these studies have led to a great diversity of opinion in regard to the erythrocyte as an osmometer

(2) The second phase is *an alteration of the form of the erythrocyte*, the shape changes caused by many hemolytic agents consist of (Ponder), first, a change from the almost perfect biconcave disk to a crenated disk the discoidal shape is gradually lost and the cell then becomes a crenated sphere, the crenations become finer and finer, and soon the cell appears to be a smooth glistening sphere, then quite quickly the glistening property of the surface is replaced by a uniform duskiness and the margin of the cell is surrounded by a brilliant diffraction band, this is known as the prolytic sphere

(3) The third phase, which occurs after a time which varies from a few seconds to a few minutes consists of escape of the hemoglobin and other cell contents into the surrounding medium, and transformation of the prolytic sphere into the almost invisible ghost, suitable methods reveal that usually the ghosts are more or less spherical in shape

When hemolysis is caused by hypotonic environment the red cell takes in water and swells to reach its "critical volume" (about 130 to 150 per cent of its original volume), the membrane then gives way, intracellular components escape and lysis is complete, this last

phase of lysis of the erythrocyte is an all or none phenomenon Some light is cast on the physical state of the hemoglobin within the erythrocyte by the observation that when an erythrocyte is fragmented in an isomotic solution the fragments retain the hemoglobin apparently with out leakage It is also significant that in hypotonic plasma the critical volume is larger than it is in hypotonic sodium chloride Furthermore the critical volume for lysis varies with the animal species and probably with individual erythrocytes of the same animal Haden has shown that there is a fairly close correlation between the thickness diameter ratio of an erythrocyte and its ability to tolerate hypotonic solutions For example the human erythrocyte has a thickness diameter ratio of 1 4 and hemolyses in 0 4 0 48 per cent NaCl, while the goat erythrocyte has a thickness diameter ratio of 1 . 1 and hemolyses in 0 72 0 74 per cent NaCl The intolerance of the spherocytes of familial hemolytic icterus to a hypotonic environment also illustrates the relationship of cell form to susceptibility to hypotonic hemolysis i e fragility sphero cytes can accept only a relatively small amount of water before they burst"

Hemolytic Agents —Hemolysis is caused in vitro by many kinds of lytic agents and physical injuries shaking freezing and thawing increase in temperature above 64 C, light in the presence of certain photochemical sensitizers ultraviolet, roentgen and radium emanations ether, chloroform the glucoside saponin bile salts and other lipoidal solvents, numerous organic solvents toxalbumins (ricin, abrin, crotin) comple ment amboceptor action enzyme reactions as in the case of lecithinases of venom and bacterial hemolysins The interesting, but not satisfactorily explained observation has been made that the susceptibility of the erythrocytes of various species to hypotonic hemolysis is inversely related to their susceptibility to saponin hemolysis In all cases studied in which the lysin is a chemical substance, it has been shown that some of it disappears at the same time that lysis of the red cell occurs Just what chemical transformation occurs is for the most part unknown, it may be quite different with different lysins, for example lysis by irradiated dyes may depend on oxidation by heat on coagulation by saponin and bile salts on a reaction with protein by bacterial lysins on enzyme reactions by venom on the action of lecithinases

Physiological Erythrocyte Destruction —Normally production of erythrocytes and destruction in the body balance each other the number of erythrocytes the amount of hemoglobin and the number of reticu locytes (0 5 to 1 0 per cent) remain constant Estimates of the daily

destruction of erythrocytes in the body vary from about 1.0 to about 4.0 per cent of the total number in the circulation Haden estimates that about 1 trillion erythrocytes wear out and are removed from the circulation each day, this would release about 28 grams of hemoglobin Other estimates yield lower figures, but of the twenty-five trillion erythrocytes in the body it is probable that not less than 1.0 per cent (two hundred fifty billion) are destroyed each day, destruction of this amount releases 7 to 8 grams of hemoglobin i e the amount of hemoglobin in 50 60 ml of blood, by other estimates the erythrocytes in about 200 to 250 ml of blood are destroyed every 24 hours Under normal conditions this erythrocyte destruction is believed to occur almost exclusively within the cells of the reticulo-endothelial system, released hemoglobin is converted by the reticulo-endothelial cells into bilirubin which is excreted in the bile The traces of heme-containing pigment present in normal human plasma are presumably formed by extracellular breakdown of a small fraction of the erythrocytes destroyed each day

Under numerous pathological conditions the rate of erythrocyte destruction is increased As much as 500 grams of hemoglobin may be liberated within 24 hours If such abnormally rapid breakdown continues to be an intracellular process, as in familial hemolytic icterus the plasma bilirubin concentration and the biliary excretion of bilirubin increase but there is little or no increase in the hemoglobin of the plasma, neither hemoglobinemia nor hemoglobinuria occurs

In the diseases and syndromes to be described briefly in the following paragraphs there is, except in the myoglobinurias excessive intravascular destruction of erythrocytes and an increase in the concentration of hemoglobin or of one of its derivatives, in the plasma If the intravascular release of hemoglobin is not too rapid, and its concentration in the plasma remains below 100 mgm per 100 ml only oxyhemoglobin is found in the plasma The reticulo endothelial system quickly removes small amounts of oxyhemoglobin, and if the plasma concentration of oxyhemoglobin does not rise above 100 mgm per ml, the kidney threshold is not exceeded and there is no hemoglobinuria If however, the erythrocyte destruction is more rapid, and, as sometimes happens the plasma hemoglobin concentration rises to 400 or 500 mgm per 100 ml other phenomena are observed the hemoglobin molecule breaks down into hematin and globin hematin and plasma albumin combine to form a new pigment methemalbumin (Fairley) Oxyhemoglobin apparently is harmless but methemalbumin is toxic it is found only after there has been a prolonged and high concentration of hemoglobin in the plasma

Methemoglobin usually is intracorpuscular and is readily reconverted to oxyhemoglobin but methemalbumin which is extracorpuscular cannot be reconverted to oxyhemoglobin presumably it is converted to bilirubin by the reticulo endothelial system What was formerly thought to be hematinemia is now known to be methemalbuminemia

In the fact that hemoglobin readily passes through the pores of the glomerular sieve and plasma albumin does not even though the molecules of the two proteins are of the same size (mol wt about 68 000) there is something of a paradox which has not been convincingly explained

As long as the concentration of plasma hemoglobin remains below 100 mgm per 100 ml, the convoluted tubles of the normal kidney reabsorb the relatively small amount of hemoglobin which appears in the glomerular filtrate and hemoglobinuria does not occur When the concentration rises above the renal threshold and the glomerular filtrate contains in a unit of time an amount (in the dog 2 3 mgm per minute) of hemoglobin beyond the reabsorptive capacity of the convoluted tubules hemoglobinuria results If the urine is alkaline the pigment is chiefly hemoglobin if acid it is methemoglobin With high concentrations of plasma hemoglobin, iron-containing pigment is deposited in the tubular cells as these cells become loaded with pigment it is believed that their capacity to absorb hemoglobin from the glomerular filtrate declines, and the renal threshold is lowered In certain persistent hemoglobinurias the tubular cells are so overloaded with pigment that they become detached and may be identified in the urinary sediment

Sulfhemoglobinaemia —Sulfhemoglobin occasionally identified in patients with enterogenous cyanosis and after certain toxic reactions due to sulfanilamide is like methemoglobin, found chiefly within the erythrocytes where it remains during the life of the cell

Myohemoglobinuria —Myohemoglobin produced by crushing injuries and also in paralytic myoglobinuria and Haff disease has a relatively small molecule (mol wt 17 500) and hence is rapidly cleared from the plasma by the kidney The renal threshold is 20 mgm per 100 ml All of these pigments are demonstrable by spectroscopic examination and by simple chemical procedures

Pathological Physiology of Hemoglobinemia and Hemoglobinuria —Recent studies of the pathological physiology of hemoglobinemia indicate that the long accepted idea in regard to the well known sequence of hemoglobinemia hemoglobinuria uremia and death probably is not correct It had been supposed that the renal failure was due to tubular

occlusion by hemoglobin casts formed in acid urine The studies of Bing indicate, however, that the accumulation of hemoglobin products in the renal tubules is a result, not the cause, of impaired renal function and decreased output Hemoglobinemia if sufficiently intense, may lead to severe kidney damage with tubular necrosis in the absence of obstructive pigment masses in the tubules This renal damage is more likely to *occur if the urine is acid Both human and animal experiments indicate* that large amounts in man up to 15 or 20 grams, of stroma free hemoglobin may be injected intravenously without apparent renal or other injury often without symptoms Infusions of very large amounts of hemoglobin seem more likely to cause tubular necrosis if the urine is acid than if it is alkaline, but even if the urine is acid, moderate amounts of hemoglobin can be excreted without demonstrable impairment of renal function There is some evidential support for the belief that concentrated hemoglobin solutions by causing spasm of renal blood vessels produce anoxia of the tubules and that this leads to impaired function anuria and uremia Ancillary factors may well be the formation of methemoglobin in acid urine, overloading of tubular cells with hemoglobin derivatives and accumulations of pigment and cells in the lumina of the tubules The role of the stromata in the immediate reactions to sudden severe intravascular erythrocyte destruction and in the later renal failure has not been satisfactorily defined

The phenomena common to all the diseases, except in very mild cases in which intravascular hemolysis is an important factor are (1) clinical jaundice (2) increased bilirubin in the plasma (3) anemia, (4) reticulocytosis, (5) increased erythropoiesis in the bone marrow and (6) splenic enlargement due to increased activity of the spleen in disposing of the remains of hemolysed erythrocytes

For other discussion of hemoglobinuria see section in Chapter XVI Vol II of Oxford Medicine entitled The Anemias

Hemolytic Transfusion Reactions

Intravascular hemolysis following blood transfusions is due to either (a) specific incompatibility between the blood of the donor and that of the recipient or to (b) non specific hemolysis such as that which may occur when blood, which has been stored too long is used for transfusion Actually the transfusion of blood from an incompatible group does not always cause a hemolytic reaction the same properties of the serum

that lead to errors in the determination of compatibility i e low titer of isoantibodies also diminish the danger of a serious hemolytic reaction By far the most frequent incompatibility causing hemolytic transfusion reactions is the presence in the donor s cells of an agglutinogen for which the recipient s plasma contains an agglutinin but there are on record a few reports of the reverse type of incompatibility such as the use of group O blood to transfuse patients of groups A B and AB To avoid this latter type of incompatibility reaction in plasma transfusions plasma from a number of donors is pooled thus high titer isoantibodies in any single plasma are diluted to a harmless titer the addition of purified solution of group substances to inactivate the isoagglutinins in plasma is another procedure which renders harmless plasma containing anti bodies for the red blood cells of the recipient slow transfusion of plasma or group O blood also minimizes the danger by promoting inactivation of the isoantibodies by tissue antigens In addition to these *intergroup* reactions there are also *intragroup* hemolytic reactions which may occur in (a) Rh negative patients who receive multiple transfusions and (b) Rh negative women pregnant with Rh positive fetuses which cause immunization of the mothers to the Rh antigen These women as a result of forming anti Rh antibodies may have hemolytic reactions when later transfused with Rh positive blood

The Rh factor is antigenically weak much weaker in fact than the A and B antigens hence the Rh incompatibility between donor and recipient may have been present at a previous transfusion but because of the low grade antigenicity of the Rh factor the isoimmunization of the recipient has been so slight that upon later transfusion of Rh negative blood serious hemolysis does not occur

The symptomatology of hemolytic transfusion reactions is subject to wide variations There may be scarcely detectable signs and symp toms in other cases there has been sudden death almost before the needle has been withdrawn A sensation of fullness in the head retrosternal and precordial oppression anxiety dyspnea are apt to be early symp toms soon followed by pain in the lumbar region The face often is suffused the neck veins are full the pulse is rapid the skin is cool and moist there may be nausea and vomiting Usually within an hour of the first symptoms there is a chill followed quickly by a steep rise in tem perature Sometimes the early symptoms, which suggest the sudden formation of a toxic substance are missing and the first manifestations of an hemolytic reaction are a chill and fever Soon after the onset of hemolytic reactions the urine is found to be dark red or of a mahogany

color due chiefly to oxyhemoglobin, if the urine is alkaline, to methemoglobin, if it is acid. Should the patient survive the phase of acute hemolysis, jaundice appears, and then there is an interval of apparent improvement during which there is oliguria, which if progressive, is ominous, failure of renal function, nitrogen retention, anuria, stupor convulsions and coma precede the uremic death, which may occur as early as the fourth day and as late as the eighteenth day. Sometimes an uncontrollable tendency to hemorrhage leads to death by exsanguination.

Treatment of hemolytic transfusion reactions should include efforts to promote diuresis by infusions of glucose and sodium chloride solutions and judicious administration of alkalis. Since the acid base regulating mechanism is seriously impaired by renal failure there is danger of alkalosis, if large doses of alkalis are administered, observations of the plasma CO_2 and pH will provide useful data on which to determine the dosage of sodium bicarbonate by mouth and sodium lactate or sodium citrate by vein. Immediate and repeated transfusions, recommended by Hesse, are probably beneficial.

A recent report by Dobbs presents evidence which seems to indicate that unilateral kidney decapsulation is quickly beneficial for the anuria following intravascular hemolysis.

Paroxysmal (Cold) Hemoglobinuria

Definition.—Paroxysmal hemoglobinuria is a rare disease characterized by transitory hemoglobinuria following exposure to cold or occasionally after exertion and by the presence in the blood of an autohemolysin which unites with the red blood cells only at low temperature. The disease is a manifestation of late syphilis either congenital or acquired.

History.—In 1854 Dressler wrote about "intermittent albuminuria and chromaturia" and set forth the first good description of paroxysmal hemoglobinuria. During the last half of the nineteenth century numerous reports appeared. The clinical features were well defined, and the disease soon became generally recognized as an entity. Donath and Landsteiner (1904) made an important contribution when they observed that the blood of these patients contains an autohemolysin which may be demonstrated by a simple in vitro test.

Etiology.—Syphilis is now accepted as the essential cause of the disease. The paroxysmal hemoglobinuric may or may not show other signs of late syphilis, but the Wassermann reaction is almost invariably positive.

Nearly all of the reported cases have occurred either in children with congenital syphilis or adults long past the secondary stage of acquired syphilis. The characteristic autohemolysin may be found in certain other syphilitics, especially in patients with general paresis who have not had hemoglobinuria.

Pathology.—Although paroxysmal hemoglobinuria is intimately related to late syphilis, it is possible by appropriate methods to remove from the blood the autohemolysin without weakening the Wassermann reaction. The titer of the autohemolysin in the serum may show variation from day to day; it may persist after the patient has ceased to have paroxysms upon exposure to cold. In the serum from different patients it shows varying degrees of thermolability. The writer has studied one patient whose autohemolysin was destroyed at 47.5° C. for thirty minutes so that fresh complement failed to reactivate it. A specimen from another patient was not destroyed at 55° C. for thirty minutes. The blood of the paroxysmal hemoglobinuric contains an isohemolysin probably identical with the autohemolysin; at least, efforts at separation have been unsuccessful.

The *Donath and Landsteiner phenomenon* reveals one of the fundamental features of the mechanism which operates during a paroxysm. The test tube reaction in its simplest form is carried out by chilling the patient's blood to about 5° C. for ten minutes and then warming it to 37° C., when hemolysis occurs. Normal blood so treated shows no hemolysis. Since the reaction requires complement, which in human blood usually is not abundant, more constant results are obtained if one separates the serum, makes a suspension (5 or 10 per cent.) of the red blood cells and adds fresh guinea pig complement. In the test tube reaction more hemolysis occurs if a heavy suspension of red blood cells is used and if the chilling is of short duration, seven to ten minutes, rather than thirty to sixty minutes. Slight union of the autohemolysin with the corpuscles may occur at a temperature as high as 16° C. With lower temperatures the union is more complete.

In the spontaneous paroxysm it seems quite probable that blood in superficial capillaries might be chilled to 15 or 16° C. Union of the autohemolysin and red blood cells then would occur. In the presence of complement hemolysis results after the chilled blood has passed from the surface of the body to the higher temperature of internal blood vessels. Hemoglobinuria follows. It has been shown, however, that attacks can be produced artificially by exposing the surface of the patient's body to a temperature (18° C.) higher than the highest temperature

at which union of the hemolysin and the red cells can be demonstrated in vitro The urinary findings occur whenever the free hemoglobin in the blood rises above the renal threshold of hemoglobin excretion In case the hemolysis is so slight that the renal threshold is not exceeded, an abortive paroxysm occurs, hemoglobinemia with mild symptoms and no hemoglobinuria, the so called "petit mal" of hemoglobinuria The appearance of *urobilin in the blood results from the increase of free* hemoglobin, the precursor of bile pigments which, in turn, constitute the mother substances of urobilin Extrahepatic formation of bile pigment or more probably, excessive production in the liver explains the slight jaundice not infrequently seen following the paroxysm Harris Lewis and Vaughan have demonstrated a dermolysin in the plasma of one of these patients The dermolysin united with the cells of the skin only at low temperatures, subsequent warming of the skin caused edema and urticaria The skin of syphilitic patients without paroxysmal hemoglobinuria could be sensitized passively to cold by intracutaneous injections of dermolysin containing serum

Recently Wagley, Zinkham and Siebens have shown that at 27 C, but not at 37 C, carbon dioxide in the presence of complement and the autohemolysin causes hemolysis of normal washed group O erythrocytes this effect of CO is inhibited by sodium cyanide and sodium sulfanilamide and apparently is not due to lowered pH alone

Symptoms —Between the chilling which may be surprisingly slight, and the onset of the paroxysm there is a *latent period* varying from a *few minutes to six or eight hours During this time the leukocyte count* may drop to 2,000 or 3,000 with a relative increase in lymphocytes With the onset of the attack the number of lymphocytes decreases and a slight polymorphonuclear leukocytosis occurs The attack consists of malaise, often headache pain in back and legs or abdomen, chilly sensations or a shaking chill transitory fever during which the temperature may be 104 F or higher and cyanosis Some patients show a temporary rise in systolic and diastolic blood pressures of 50 to 100 mm of mercury Frequently the liver and spleen enlarge during an attack In a few cases the phenomena of Raynaud s disease or other manifestations of vasomotor disturbance such as urticaria or vesicular lesions are associated with the attacks The urine is dark red or Burgundy color often described as black by the patient It contains hemoglobin methemoglobin hematin hyaline, granular and pigment casts and urobilin The presence of the pigment, uro-erythrin has been demonstrated also In these cases the urine is rose colored In freshly passed specimens intact erythrocytes

may be found The hemoglobin may be present in only one specimen of urine, or it may persist for a day or two Following the attack *mild jaundice* is common In the interval between attacks the patient may be in good health but not infrequently there are symptoms due to other manifestations of late syphilis When attacks have been repeated at short intervals *secondary anemia* is commonly present

Diagnosis —The history of transitory excretion of dark colored urine during the winter months following exposure to cold or rarely exertion a positive Wassermann reaction and stigmata of late syphilis the Donath and Landsteiner reaction in the drawn blood and the artificial production of an attack by immersion of hands or feet in ice water provide the data which establish the diagnosis Without a positive Wassermann reaction the diagnosis is uncertain

Treatment —Various forms of therapy have been advocated auto serotherapy (Widal Abrami and Brissaud) graded cold foot baths (Salen) and administration of calcium chloride or calcium lactate These forms of treatment lack a rational basis and have not been demonstrated to compare in effectiveness with antisyphilitic treatment which Kumagai and Namba in a study of 14 patients have clearly shown to be the method of choice The writer observed two patients who after thorough anti syphilitic treatment passed through two consecutive winters in New York City without an attack In each case however the Wassermann and the Donath Landsteiner reactions remained positive although weal ened The patients were treated with many arsphenamine injections mercury iodides and bismuth This result corroborates the observations of Jones and Jones and others It will be of interest to know how penicil lin therapy works in such patients

Paroxysmal Nocturnal Hemoglobinuria (Marchiafava Michele Disease)

First described as a disease entity by Marchiafava and Nazari in 1911 only 50 cases of paroxysmal nocturnal hemoglobinuria had been reported up to 1946 It is non hereditary, equally distributed between the sexes has its greatest age incidence in the third and fourth decades but has been observed in a child of five and a woman of 5 The onset is insidious in the early stages there may be only a persistent anemia without hemoglobinuria The disease is characterized by an hemolytic anemia with hemosiderinuria and urobilinogenuria by great chronicity

by exacerbations and remissions and especially by the curious occurrence of intravascular hemolysis and hemoglobinuria which occur chiefly during sleep. The usual symptoms are weakness, fatigability, slight jaundice and the excretion during the night and the early hours of the morning of dark, often almost black, urine. During exacerbations chills, fever, malaise, abdominal and lumbar pains may occur. Often there is moderate enlargement of the liver and spleen. The red blood cell count usually is between 2,000,000 and 3,000,000 but during exacerbations may be lower; there is moderate macrocytosis, the mean corpuscular hemoglobin concentration is normal; there is a reticulocytosis up to 20 or even 30 per cent; leukopenia and thrombocytopenia are usual; the differential count may be quite normal, but more often a neutropenia causes a relative lymphocytosis. The red blood cells are normally resistant to hypotonic salt solutions but abnormally susceptible to acidified plasma (Van den Bergh, Ham), the Donath-Landsteiner test and the complement fixation reaction for syphilis are negative.

Two presumptive determinants of the intravascular hemolysis in this disease have been identified: the sensitiveness of the red blood cells to increased hydrogen ion concentration revealed by the "acid hemolysis test" (Ham) and a thermolabile plasma component similar to or identical with, alexin which is essential for the occurrence of hemolysis under conditions in which normal erythrocytes are not hemolysed. The essential abnormality in this disease, in contrast with the pathological basis for the hemolysis in paroxysmal cold hemoglobinuria, resides in the erythocytes; the abnormality is associated with an increased susceptibility to hemolysis by lowered pH, but there is no evidence that the pH of plasma falls during sleep to a level at which the red blood cells of those patients are hemolysed in vitro; this is reminiscent of the absence of evidence in familial hemolytic icterus that the red blood cells are ever exposed in the body to a hypotonic solution. The hemolytic mechanism of this disease does not involve, according to Manchester's observations, the formation of spherocytes prior to lysis.

Renal blood flow, glomerular filtration and tubular function may even in severe cases be unimpaired. The principal gross and microscopic changes in the organs, in addition to the anemic aspect and icterus, are mahogany colored kidneys, the cortices of which give a Prussian blue reaction; iron-containing pigment in the cells of the renal tubules; in the liver, spleen and bone marrow less than the normal amount of iron is found. This distribution of iron pigment is found in no other hemolytic anemia. The bone marrow shows a normoblastic hyperplasia. The dis

ease is apt to be complicated by frequent infections and thromboses No known treatment modifies more than temporarily the course of the disease Alkalinization is not beneficial splenectomy is worse than useless Transfusions even though they may intensify the hemoglobinuria will often help to tide a patient over an exacerbation

Blackwater Fever

This form of hemoglobinuria is discussed in Chapt XXII B Vol V of Oxford Medicine

March Hemoglobinuria

This relatively benign form of hemoglobinuria is observed only in young adult males after marching walking or running Symptoms other than hemoglobinuria are mild or absent Hemoglobinemia precedes the hemoglobinuria In some cases a lumbar lordosis or a lordotic posture while marching seems to have pathogenetic importance There is neither anemia nor reticulocytosis the patients are non-syphilitic the white blood cell and platelet counts are normal no isohemolysins or auto-agglutinins have been demonstrated nor has any abnormality of the erythrocytes been detected The pigment in the plasma during attacks is oxyhemoglobin in the urine also it is chiefly oxyhemoglobin The red blood cells in 6 to 40 ml of blood are destroyed intravascularly in an attack The renal threshold for hemoglobin appears to be lower in these individuals than in normal persons The disease is self limited spontaneous recovery may be expected within a few months or at most in a few years

The Myoglobinurias

The Crush Syndrome —Recognized first by the Germans (Minami) in World War I the crush syndrome was a frequent condition in 1940 among air raid casualties in England People buried under beams masonry and debris of collapsed buildings with heavy crushing of one or more extremities for several hours often upon release from the compression exhibit a sequence of clinical phenomena which falsify the

favorable prognosis which may be suggested by the apparently good condition of the individual when rescued Very soon after release the compressed extremities swell, become paralyzed and insensitive, blood volume decreases, pallor, weakness, sweating, thirst and low blood pressure follow Shock treatment often brings about marked improvement and again the patient appears, deceptively, to be on the way to recovery Progressive oliguria foreshadows severe renal failure with marked nitrogen retention, rising blood pressure

Urine passed after release of the compression contains oxymyoglobin and metmyoglobin which have leaked out of the traumatized muscle cells, the urine is very acid and contains a brown precipitate identified as acid hematin Potassium and creatinine diffusing into the blood stream from the crushed muscle fibers are present in high concentration in specimens of urine passed shortly after release from the crushing force With progressive impairment of renal function potassium is retained

Death is apt to occur on the sixth or seventh day it is thought to be due to renal failure and cardiac arrest from potassium poisoning Post mortem examination reveals necrotic muscle with fish flesh' appearance in the crushed areas and kidneys in which the convoluted tubules are necrotic and many of the tubular lumina contain casts of myoglobin The glomeruli appear unaltered The relative importance of compression, muscle necrosis and myoglobinuria in the pathogenesis of the renal failure is not entirely clear but myoglobin in an acid urine appears to be one perhaps the principal, etiological factor

Once the syndrome is fully developed treatment modifies the course of events very little, if any Transfusion of blood or plasma during the shock phase is of great value and before oliguria is marked discriminating administration of alkali and adequate fluid to maintain urinary volume are indicated The use of insulin and dextrose to lower the potassium contrentration of the blood has been recommended (Bywaters)

Further discussion of the crush syndrome will be found in the the chapter on Bright s Disease Chap X Vol III

Paralytic Myoglobinuria—Work horses kept on a high carbohydrate diet during a rest period sometimes upon resuming heavy work, develop paralytic myoglobinuria, chills, fever and uremia The concentration of plasma potassium rises, and if death does not occur, there is often residual paralysis Post-mortem examination shows pale edematous muscles with fish flesh appearance and necrosis of renal tubules with myoglobin casts in the lumina of the tubules Eight cases of the

same disease have been reported in man The clinical phenomena and the gross histopathology are very similar to those of the crush syndrome The pathogenesis is not well understood but it has been suggested that the resting muscles store up excessive amounts of glycogen and upon resumption of heavy work injurious amounts of lactic acid are formed within the muscle cells

Haff Disease —A disease characterized by a similar symptomatology and pathology is the "*Haffkrankheit*" which occurred among people in Konigsburg Germany, who ate fish or eels from the adjacent inlet (Haff) Paroxysms of pain in striated muscles with stiffness and limitation of motion occur, the urine is dark red or black due to the presence of myoglobin At autopsy the muscles are necrotic and have the "fish flesh" appearance It is believed that the fish and eels were poisoned by waste products perhaps arseniuretted hydrogen from cellulose factories and that affected individuals absorbed from these sea foods the toxic substance which releases myoglobin

Favism

This disease, geographically highly selective is characterized by an acute often severe hemolytic anemia resulting from the ingestion of the green seeds of the fava bean (*Vicia faba*) or from inhalation of the pollen So far as is known it occurs very rarely outside of Sardinia and Sicily, where many cases occur and certain parts of the Italian mainland Its incidence seems to be influenced by racial and familial factors It occurs in both sexes and at any age but is most serious in infants and children in whom the case fatality rate may reach 8 per cent The symptoms are those of a rapid and extensive intravascular hemolysis Chills fever vomiting pain in the back and a rapidly ingravescent anemia are characteristic Within a few hours hemoglobinuria and deep jaundice occur Occasionally the acute attack is followed by oliguria renal failure uremia and death Allergy to components of the fava bean is said to be an important factor in pathogenesis For additional discussion see Chapt XXX, Vol II of Oxford Medicine

Hemoglobinuria of Burns

Severe burns may cause hemoglobinemia hemoglobinuria and some degree of impaired renal function Shen Ham and Fleming have shown

that the blood of burned patients may contain fragmented erythrocytes and spherocytes with increased susceptibility to osmotic hemolysis Intravascular destruction of the fragile cells is therefore the explanation of the hemoglobinuria

Toxic Hemoglobinuria

Occasionally the sulfonamides, especially sulfanilamide, cause an acute sometimes fulminating hemolytic anemia with hemoglobinuria, the mechanism is obscure Very large abortifacient doses of quinine have caused a fatal hemolytic anemia with hemoglobinuria Numerous organic and inorganic poisons taken by mouth in adequate doses have been known to cause hemoglobinuria, e g potassium chlorate phenyl hydrazine turpentine, oxalic and chromic acids Arseniuretted hydrogen snake and spider venoms also are known to be hemolytic and capable of causing hemoglobinuria

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CHAPTER XXII

LEUKOPENIA

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INTRODUCTION

Definition — Leukopenia signifies a scarcity of leukocytes in the peripheral blood Since the normal leukocyte count varies within a fairly wide range what is leukopenia for one individual under a given condition may be quite normal for another Thus an exact figure for normality cannot be given although it can be stated that the normal range is from 5 000 to 10 000 per cu mm The lower value is not uncommon in the basal state as Garrey and his collaborators[1] have demonstrated During the daily stress and strain of existence the leukocyte count usually increases from its initial low value to about twice that amount It is prob

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able that the lowest values are obtained in the most sluggish individuals at their lowest ebb of muscular activity Thus, in a study of schizophrenia the lowest counts were obtained in the so called hebephrenic patients, who generally were content to sit about almost motionless the entire day In the more active cases the counts tended to be higher

Each individual seems to have his own standard leukocyte count Thus a count of 4,000 per cu mm may be quite normal for one person, whereas a similar count in an individual whose normal value is 8,000 per cu mm is distinctly low With these reservations in mind nevertheless one may make the following tabulation

White Blood Corpuscles	5,000 to 6 000	borderline leukopenia
	4 000 to 5,000	fairly definite leukopenia
	less than 4,000	definite leukopenia

Causes of Leukopenia

To appreciate why the leukocyte count becomes lower than normal requires an understanding of the physiology of leukocyte formation and distribution The leukocyte count in the peripheral or circulating blood is a composite of cells derived from the three blood forming organs the bone marrow the lymphoid tissue and the reticulo endothelial system In these scattered tissues cells are produced, mature and then are emitted into the blood stream The exact number of cells which is actually delivered into the circulation must depend on several factors (Table I) (a) the total mass of the blood forming tissues (b) their rate of cellular growth and maturation (c) the extent of the demand by the various tissues for a specific type of cell (d) the rate of emission or delivery of cells from the blood forming tissues to the blood The leukocyte count is influenced further by the degree of hoarding sequestration or redistribution of cells in various tissues and by the rate of breakdown in the tissues or in a locus of disease

A normal leukocyte count presupposes therefore (a) adequate well functioning blood forming tissues, (b) a well functioning delivery mechanism and (c) a normal rate of cellular sequestration and destruction in the tissues

The normal leukocyte count is a variable figure which depends upon many physiologic factors Factors which tend to raise the normal count are exercise heat, excitement, meals (?) pregnancy and hemoconcentration Conversely, lower counts are obtained at rest during periods of fasting and with hemodilution In general an abnormally low leukocyte count may be due to (a) an inadequacy or hypofunction of one or all of the blood forming tissues (b) a disturbance in the delivery mechanism or (c) an unusual rate of cellular sequestration or destruction in the tissues

TABLE I

A CLASSIFICATION OF LEUKOPENIA WITH PARTICULAR REFERENCE TO ETIOLOGICAL FACTORS

A *Bone marro Disturbances*

1 Aplasia
Hypoplasia } Aplastic Anemia

a Due to Chemicals Benzol
Benzene containing Drugs
Toluol
Radium
Radioactive Substances including Thorium Mesothorium Thorotrast etc
X rays
Gold Salts
Other Chemicals Sulfonamides Aniline etc

b Toxic
Nephritis
Unknown causes

c Diminished Need
Hypometabolism of Myxedema
Old Age
Prolonged Undernutrition

2 Invasion or Replacement by Foreign Tissue
Leukemia
Lymphosarcoma
Reticulum Cell Sarcoma
Plasmacytoma (Multiple Myeloma)
Gaucher s Disease
Generalized Hodgkin s Disease (Reticulosis)
Fibrosis secondary to von Recklinghausen s Di ease
occasional cases of Hodgkin s Disea e
Osteosclerosis Polycythemia — certain cases of
Marble Bone Disease

3 Maturation Arrest of Leukocytes
a Deficiency States Pernicious Anemia Chronic Iron Deficiency
b Allergic Reactions associated with Drugs particularly Aminopyrine
Digestive

B *Disturbances in the Delivery Mechanism*

1 In certain severe cases of sepsis

2 In certain acute or subacute infections in which the reticuloendothelial sy t m and the spleen are particularly involved
Typhoid Fever
Malaria
Histoplasmo is
Miliary Tuberculosis etc

3 In cases of Hyper plen m
Cirrhosis of Liver

nuclear leukocytosis of mild degree This is accompanied by an increased proportion of immature polymorphonuclears, including myelocytes and a variable number of nucleated red cells

Reticulum cell sarcoma and generalized or aleukemic reticulosis, the latter closely allied to Hodgkin's disease may result in similar pictures although here monocytosis may be present together with an occasional histiocyte Plasma cytosis or multiple myeloma, fibrosis of the marrow, osteosclerosis, etc may result also in pancytopenia

The differential diagnosis of these conditions from aplasia of the marrow often is very difficult In the presence of an irregular or Pel Ebstein relapsing fever reticulosis or generalized Hodgkin s disease is probable In many cases a final diagnosis can be made only by biopsy of the sternal marrow Although a simple needle aspiration is sufficient in most cases, the removal of a small button of bone by means of a trephine may be required when the aspirated material is unsatisfactory for diagnosis[1]

Maturation Arrest of Granulocytes in the Marrow —*Deficiency States* —The piling up of large numbers of immature granulocytes in the marrow without any evidence of leukemic proliferation the blood meanwhile showing a diminished number of leukocytes was termed maturation arrest by Fitz Hugh and Krumbhaar in 1935[13] The condition is seen most commonly in certain deficiency states notably in *pernicious anemia* in which due to a lack of sufficient liver extract factor the various blood forming functions of the marrow are impaired Erythropoiesis becomes megaloblastic and leukopoiesis becomes greatly modified with bizarre and giant metamyelocytes dominating the marrow picture[14] From the leukocytic standpoint this is reflected in the peripheral blood by the presence of leukopenia and granulocytopenia The leukocyte count usually varies from 1 000 to 5 000 per cu mm and the polymorphonuclears from 20 to 50 per cent with many multilobulated forms, the so called P A neutrophiles The erythrocytic picture of predominant macrocytosis with well marked changes in size and shape of the red cells is well known, and there is a great reduction in the platelets

Following the institution of liver extract therapy the character of the marrow picture changes sharply The abnormal megaloblastic type of erythropoiesis changes to a normoblastic variety and the bizarre metamyelocytes disappear[14] In the blood not only does reticulocytosis occur but the leukocytes normal granulocytes and platelets become greatly increased

In *chronic iron deficiency* leukopenia and granulocytopenia are common also with white cell counts of 2 000 to 4 000 per cu mm often being present[15] Following the institution of iron therapy the leukocytes and granulocytes rise quickly to normal

Allergic Reactions — Drugs — The extreme hypersensitivity on the part of certain individuals to such chemicals as amino pyrine with resultant leukopenia and granulocytopenia is by now well known (see in next chapter on Agranulocytosis) In this reaction the granulopoietic tissue of the bone marrow acts as the chief shock organ Although aminopyrine appears to be the most important of these sensitizing drugs arsenic arsphenamine neoarsphenamine the sulfonamide drugs etc also may be productive of granulocytopenia probably because of similar mechanisms Reduction in leukocytes often is extreme with counts of 500 to 1 000 per cu mm being common Granulocyte proportions greater than per cent are rare and usually fewer granulocytes are seen the remainder of the cells usually are mature lymphocytes There is no anemia or thrombopenia

Digestive — Milder forms of leukopenia which also are thought by some to be on an allergic basis have been described Thus Keuthe[1] (1907) described leukopenia in certain individuals following an unusual ingestion of fat albumin or carbohydrate Widal Abrami and Jancovesco[1] (1920 and 1921) described a hemoclastic crisis with leukopenia following the ingestion of 200 gm of milk in individuals with liver disease As a test for liver function the concept proved of no value E F Muller (1933)[1] in studying a number of patients who had developed leukopenia following injections of arsphenamine found that several of them later developed well marked leukopenia following the ingestion of 200 gm of milk Vaughan[9] (1933 and subsequently) suggested that Widal s hemoclastic crisis might be used as a test of the allergic sensitivity of certain individuals to milk He then extended his observations on milk to include various other foods and suggested a leukopenic index as a diagnostic method in the study of food allergy In the technique of the test leukocyte counts at 10 minute intervals were performed on a fasting patient The food to be tested then was eaten following which three additional leukocyte counts at 10 minute intervals were performed If any of the postprandial counts were 1 000 or more less than the lowest initial count the result was said to indicate a food allergy These results although soon confirmed by various observers have been criticized frequently[6] That a definite leukopenia occasionally occurs in certain individuals who are unusually susceptible to such foods as milk appears certain but that a variation of 1 000 or so leukocytes in a period of one or two hours after the ingestion of a food is significant of an allergic hypersensitivity is to be doubted

Disturbances in the Delivery Mechanism

The mechanisms relating to the emission or delivery of the white cells from the bone marrow to the peripheral blood are quite obscure It is the generally accepted teaching that leukocytes arise from just outside the sinusoids of the

marrow, the most primitive types being closest to the endothelium lining the capillary.[1] The most mature leukocytes are thought to enter the sinusoids through their active motility although it should be noted that this is based on little more than speculation. Very little is known of the factors governing the speed of growth of the leukocytes and their delivery into the circulation. Undoubtedly chemical influences in the tissues play a role, without them it is possible that the normal leukocyte count might be considerably less than approximately 7 000 per cu mm. This is perhaps borne out by the type of differential count seen in infancy and childhood in which the granulocyte count is quite low.

LEUKOPENIA OF SEVERE AND OVERWHELMING SEPSIS — Most infections, particularly of the pyogenic type are associated with a well defined increase in leukocytes this has been shown by Menkin to be due to the development in the infected tissue of a substance which he has called leukotaxin. The entrance of this substance into the blood stream appears to result in the stimulation of leukocytic growth in the bone marrow and in the delivery of large numbers of polymorphonuclear cells into the blood stream. There is thus no dissociation between stimulation, growth and delivery of granulocytes. However in certain very severe cases of pyogenic infection particularly those with fulminating sepsis, the leukocyte count may become lower than normal. The leukotactic stimulus in these cases probably is present in as great or even greater fashion than ordinarily, which indicates that either a disturbance in maturation or in the delivery mechanism is present. That the latter is probable is seen in the large numbers of both very early and relatively mature leukocytes in the bone marrow indicating that maturation is normal. Furthermore, differential counts of the white cells in the blood under these conditions show a great relative increase in the metamyelocytes with occasional myelocytes and mature polymorphonuclears. These cells are therefore being produced normally, but their delivery has been impaired.

Whatever the exact mechanisms may be there results (1) a gradually developing leukopenia which is associated with (2) a well marked polymorphonuclear leukocytosis and the presence of many band and young forms and even myelocytes and myeloblasts in unusually severe cases and (3) with extreme degrees of toxic change in the polymorphonuclear cells. The cytoplasm often becomes bluish the granules coarse irregular widely spaced and often basophilic vacuolization of the cytoplasm not infrequently is present. The latter is of serious prognostic import.

Schilling[3] has termed the phenomenon of leukopenia in association with the presence of many immature polymorphonuclears the degenerative shift in contrast to the regenerative shift seen in the usual and uncomplicated pyogenic infections. The term degenerative implies a degeneration of granulopoiesis in the

marrow, which is not borne out by actual marrow studies The presence of marked toxic changes of the granulocyte series in both the marrow and the blood probably indicate a direct antigen antibody reaction within the granulocyte with resultant qualitative changes

The leukopenia of overwhelming sepsis must be distinguished from that which not infrequently develops with administration of one of the sulfonamide drugs Since cases of severe sepsis now are given these drugs almost routinely the question often arises whether the development of leukopenia is due to drug or to sepsis solution of this problem may be very important since upon it depends the further therapy of the case at hand and perhaps the patient s ultimate prognosis In drug leukopenia there is usually a progressive decline in both mature and immature granulocytes In the leukopenia of severe sepsis the granulocyte percentage is greatly elevated immature cells are numerous and toxic changes are marked However combinations of leukopenia due to sepsis and drug may be present making differential diagnosis difficult if not impossible Further use of the drug then may become a matter of careful clinical judgment and evaluation of all the factors concerned If sepsis is severe and progressive and of the type streptococcal pneumococcal meningococcal etc which is benefited ordinarily by use of the drug it is probably best to continue its use If on the other hand, such treatment seems questionable the drug should be di continued by all means

Leukopenia due to sepsis occasionally may be mistaken for true agranulocytosis In the latter total white cell counts above ooo per cu mm are unusual and there is usually a complete lack of granulocytes although in some cases a few immature granulocytes may be present In sepsis however the total leukocyte count usually is between 2 000 to 4 000 with from 20 to 50 per cent granulocytes Likewise septic leukopenia may be mistaken occasionally for leukemia although generally the reverse is true Both acute leukemia aleukemic and overwhelming sepsis are present in very sick looking feveri h individuals in whom anemia becomes rapidly progressive Petechial and hemorrhagic disturbances although fairly common in severe sepsis are outstanding in acute leukemia as are marked gingival changes The blood picture of sepsis although it shows many immature cells metamyelocytes and occasionally myelocytes differs sharply from that of acute leukemia in which large numbers of primitive cells blasts of one form or another are present

LEUKOPENIA OF NON PYOGENIC INFECTIOUS STATES — Although the leukopenia of infectious states (Table II) has been known and utilized diagnostically for many years its recognition was delayed for some time since attention naturally was attracted first to the commonly found leukocytosis Thus Hayem [4] in his well known text of 1889 dismissed leukopenia with scant mention saying it

was very rare In v Limbeck s ponderous text book of hematology (1896) there is no mention of leukopenia Thayer [6] of this country, however, collected 826 leukocyte counts in typhoid fever and was one of the first to point out the diagnostic value of leukopenia in this disorder In Cabot's text [7] (1897) mention is made specifically that of the various infective diseases grippe, measles miliary tuberculosis, malaria and typhoid fever were often associated with leuko

TABLE II

INFECTIONS WITH LEUKOPENIA

A *Pyogenic with Polymorphonuclear Response*

1 Severe fulminating streptococcus staphylococcus pneumococcus meningococcus infections
   Spreading sepsis septicemia peritonitis etc
   Usually of poor prognostic omen
2 Last stages of convalescence of some pyogenic infections
3 Chronic pyogenic infections abscesses collections of pus in small areas etc
4 Acute miliary tuberculosis

B *Lymphoid with Lymphocytosis*

1 Last stages of convalescence of some pyogenic infections and in chronic pyogenic infections
2 In certain chronic infections tuberculosis syphilis malaria undulant fever
3 In infections directly involving the lymphoid apparatus
   Infectious Mononucleosis (certain cases)
   Infectious Lymphadenitis (non specific)
   Tuberculous Lymphadenitis
   German Measles eruptive stage

C *Reticuloendothelial with Monocytosis*

Typhoid Fever
Malaria
Tuberculosis (certain cases particularly rapidly progressive especially miliary tuberculosis and in children)
Kala azar and other Leishmanias
Trypanosomiasis
Histoplasmosis of Darling
Syphilis (certain cases particularly with hepatosplenomegaly)
Subacute Bacterial Endocarditis
Undulant Fever

D *With No Particular Tissue Response Usually Virus Infections*

Influenza Grippe
Primary atypical (virus) pneumonia certain cases
Mumps
Psittacosis
Measles
Tularemia
Dengue

penia With the great increase in the use of the leukocyte count beginning with the turn of the century numerous infectious conditions were discovered in which leukopenia was often or invariably present (Table II) This soon proved of great diagnostic value since the pyogenic infection were associated almost invariably with leukocytosis Thus the presence of leukopenia in an infectious state pointed to infectious diseases other than those which were pyogenic in nature From the standpoint of their effect on the blood cells it is probable that there are in general at least 5 types of infectious diseases those associated (1) with a neutrophilic polymorphonuclear response (2) with lymphocytosis (3) with monocytosis (4) with eosinophilia and (5) those in which no particular leukocytic response is evoked Leukopenia customarily does not occur in the first or the fourth group in both of which a granulocytic bone marrow response is present However a reduction in leukocytes i quite common in those infections associated with lymphocytosis monocytosis or tho e in which no particular leukocytic response is present

The reciprocal relationship of the polymorphonuclears to the lymphocytes is well brought out in infectious states Thus in acute pyogenic infections with a sharp increase in neutrophiles the lymphocytes are strikingly reduced Conversely, when the infection is subsiding and the lymphocytes become increased the polymorphonuclear cells become reduced At this stage the total white count may even become reduced if the infection continues to smolder along leukopenia almost always develops

In *infections commonly associated with lymphocytosis* leukopenia is often present (Table II) providing the absolute increase in lymphocytes is not sufficiently great to cause in and of itself a rise in the white count Thus *infectious mononucleosis* the prime example of a lymphoid type of infection not infrequently is associated with leukopenia rather than with the usual leukocytosis This occurs in from 5 to 10 per cent of all cases in some instances the leukopenia may be so marked 1 000 to 2 000 and the proportion of lymphocytes so high 80 to 90 per cent that the diagnosis of agranulocytosis may be entertained (see in next chapter on Agranulocytosis) The presence of from 5 to 10 per cent of neutrophiles the generalized lymphadenopathy and the lack of severe constitutional symptoms tend to rule out this condition further confirmation usually being obtained by means of the heterophile agglutination test

Rubella German measles resembles infectious mononucleosis in many respects and often is indistinguishable hematologically from it In both conditions there are generalized lymphadenopathy and well defined lymphocytosis Leukopenia is present frequently in the eruptive stage of rubella the lymphocytes usually are variable in size shape and staining characteristics

Lymphocytosis also occurs in the *terminal stages of acute infections in vari-*

ous chronic infectious processes, tuberculosis syphilis, malaria, undulant fever, etc, and not infrequently is associated with a low total leukocyte count The cause of the leukopenia in these conditions is not readily apparent, but it seems likely that the same stimulus which evokes a lymphocytic response simultaneously results in either a reduction in granulocyte production or in their delivery from the bone marrow to the blood The latter possibility appears most likely, since studies of the sternal marrow show no lack of granulocytes but rather a hyperplasia of these elements

Conditions with monocytosis also not infrequently are associated with a leukopenic response An increase in blood monocytes is presumably indicative of reticuloendothelial proliferation in response to various types of infectious agents This occurs in the beginning convalescent stages of acute pyogenic infections and in such conditions as typhoid fever malaria, many cases of tuberculosis and undulant fever certain cases of syphilis kala azar and other leishmanias trypanosomiasis histoplasmosis subacute bacterial endocarditis, Boeck's sarcoid, etc In the presence of monocytosis histiocytes may also be found It is to be noted that the spleen becomes enlarged in most or all of these conditions, and it is possible that this enlargement may be responsible for the development of the leukopenia As stated in the next section the spleen probably has inhibitory effects on the bone marrow production and delivery of leukocytes With splenomegaly from diverse causes leukopenia often is present and continues as long as there is splenic enlargement or until splenectomy is performed It is, therefore possible either that the reticuloendothelial hyperplasia itself results in an inhibition of leukocytic growth or delivery or that the enlarged spleen has *hypernormal effects on these functions with resulting leukopenia*

In *infections in which no particular type of white blood cell appears to be involved* leukopenia may be present This is seen often for example in such virus infections as influenza primary atypical or virus pneumonia and psittacosis So called grippe which is quite mild and lasts from 1 to 3 or 4 days, frequently is associated with leukopenia

LEUKOPENIA OF SPLENIC DISORDERS — The spleen as noted already appears to have an inhibitory effect upon the cells of the bone marrow more particularly on the white cells and platelets [5] This effect becomes apparent in many cases in which splenomegaly is present The evidence pointing to an inhibitory effect of the spleen on leukocytic production maturation or delivery at present must be considered circumstantial since no definite proof of this has been formulated as yet These circumstantial indications are as follows (1) leukocytosis following splenectomy in normal humans post traumatic splenectomy, and in animals, (2) leukopenia in many cases with splenomegaly, in association with (3) well defined leukocytic bone marrow hyperplasia with return of the bone marrow

picture and the leukocyte level to normal following splenectomy The evidence from these studies is in favor of a plenic control of the emission of mature leuko cytes from the bone marrow to the circulating blood

Symptomatic Splenic Leukopenia —Splenic leukopenia may be either sec ondary to some known cause i e symptomatic or primary or idiopathic The symptomatic cases are by far the most common and well defined primary cases have been described only recently, and their complete acceptance must await further studies

Chronic Congestive Splenomegaly Portal Hypertension including Cirrhosis of the Liver the Banti Syndrome etc —Leukopenia is a common accompani ment of cirrhosis of the liver That it is associated with the splenic enlarge ment which is present so commonly appears probable because of the marked rise in white cells which occurs following splenectomy Chronic hepatitis cirrhosis results in congestion within the portal circulation and in an increase in the portal venous pressure Splenomegaly probably is due to the portal hypertension and the pancytopenia which frequently ensues anemia leukopenia thrombocytopenia probably is the end result of the splenomegaly and not of increased portal venous pressure Portal hypertension occurs not only in cirrhosis but in obstructive dis orders of the portal vein itself, pyelephlebitis neoplasms compressing the branches of the portal vein and splenic vein thrombosi A list of such dis orders as given by Thompson [8] and by Rousselot[2 ( )] includes the following con ditions

- I *Obstructive factor known*
  - A Cirrhosis of the liver
    - a Laennec s cirrhosis
    - b Unclassified cirrhosis
    - c Cirrhosis due to schistosomiasis mansoni
  - B Thrombosis of the splenic vein
  - C Cavernomatous transformation of the portal vein
  - D Stenosis of the portal vein
- II *Obstructive factor undetermined*

The so called Banti s disease or Banti s syndrome must be included in this list In all probability as pointed out by many observers this condition is a waste basket entity including such conditions as cirrhosis of the liver splenic vein thrombosis chronic malarial splenomegaly chronic infectious including syphi litic and tuberculous splenomegaly, certain cases of Mediterranean anemia and even certain instances of primary neoplasms of the spleen

Particular attention should be paid to cases with splenomegaly leukopenia and hematemesis occurring in children In a child or a young adult in whom

vomiting of blood or melena or both occur, and in whom the leukocyte count immediately following hemorrhage is either normal or only slightly elevated, the possibility that splenic vein thrombosis is present should be considered, since the normal reaction to severe hemorrhage especially in a young individual, is that of marked polymorphonuclear leukocytosis These cases are characterized by splenomegaly, leukopenia, the tendency to severe gastro intestinal bleeding and thrombotic manifestations within various parts of the portal venous system[30] The gastrointestinal bleeding apparently is due to dilatation and rupture of the vasa brevia of the stomach and not to the development of over distended collateral esophageal veins Following hemorrhage palpation of the spleen frequently is difficult and often the only evidence of possible splenic disease is the lack of well marked leukocytosis In a few days to a week after the initial hemorrhage the spleen may become palpable and the leukocyte count low

The various conditions just referred to usually are associated with a leukopenia of from 1,000 to 5,000 per cu mm There is generally a proportionate reduction in the granulocytes to between 30 to 50 per cent, but the relative number of polymorphonuclears may be normal thus the absolute number of granulocytes almost always is decreased The polymorphonuclears usually are immature and multilobulated forms are seen often

Removal of the spleen in these conditions results in a well defined increase in leukocyte count often to leukocytic values 10 000 to 15,000, although a rise simply to normal values is not unusual

Chronic Enlargement of the Spleen without Evidence of Portal Hypertension — Splenomegaly is a common accompaniment of certain infections typhoid fever brucellosis malaria kala azar trypanosomiasis histoplasmosis and occasionally is seen in tuberculous or syphilitic involvement of the spleen and in subacute bacterial endocarditis A leukocyte count of 1,000 to 4 000 per cu mm is present commonly The granulocytes usually are reduced to levels of 20 to 50 per cent and a monocytosis of 15 to 30 per cent is common Often this is associated with the presence of histiocytes which have a characteristic morphologic appearance [1] They are very large cells from 15 to 30 micra, quite irregular in size often with pseudopodia and frequently vacuolated The cytoplasm is light blue in color with coarse violet granules grouped about a round nucleus which has a thick perinuclear membrane and is made up of a spongy chromatin meshwork

The severe leukopenia of *kala azar* is one of a diagnostic triad which includes splenomegaly and hyperproteinemia Final diagnosis is made by splenic or marrow puncture and the finding of Leishman Donovan bodies[2] In the *histoplasmosis of Darling*[33] there is generalized lymphadenopathy and splenomegaly with marked leukopenia the lymph nodes, sternal marrow and spleen show

Leishmania like bodies *Tuberculous splenomegaly* may be the end result of a chronic miliary tuberculosis As Englebreth Helm[44] has pointed out the only diagnostic evidences of this may be the finding of splenomegaly and leukopenia in association with old tuberculous lesions of the lungs In one case which I observed actual tubercles in the surface of the spleen confirmed later at operation were observed at peritoneoscopy *Syphilitic splenomegaly* usually is associated with syphilitic involvement of the liver and has been called by Stokes[5] syphilitic hepato plenomegaly These cases which occur in latent or tertiary syphilis are characterized by irregular enlargement of the liver syphilitic cirrhosis plenomegaly leukopenia and a persistently positive serological test for syphilis They often show a persistently positive serological reaction after intensive therapy and may be benefited by splenectomy which Stokes has shown may result in a negative serological test *Subacute bacterial endocarditis* usually accompanied with leukocytosis may particularly in cases with marked splenomegaly be associated with leukopenia

Rheumatoid arthritis at times is associated with splenomegaly and marked leukopenia This has been called *Felty's*[6] *syndrome* and has been the occasion for much discussion regarding its pathogenesis In a typical case (Una S) recently observed, rheumatoid arthritis had been pre ent for about 15 years for the last few years menorrhagia and many disabling infections with high fever and leukopenia had been present A year previously splenomegaly had been discovered for the first time on examination the spleen was found to extend almost to the brim of the pelvis the liver was not enlarged and there was no evidence of cirrhosis The blood showed slight normochromic anemia moderate thrombocytopenia 100 000 per cu mm and marked leukopenia of between 800 to 1 000 per cu mm with 5 to 10 per cent granulocytes Examination of the sternal bone marrow disclosed de pite the leukopenia marked hyperpla ia of the granulocytes with an ncreased number of immature forms There was evidently maturation arrest or an inhibition of delivery Whatever the mechanism the severe leukopenia in the circulating blood was thought to be an important factor in the development of the numerous infections from which the patient suffered Spenectomy therefore was determined upon This was carried out uneventfully and was followed by a rise in the leukocytes to normal elimination of further infections and cessation of menorrhagia

Felty s syndrome thus is a form of splenic leukopenia which apparently occurs as the result of involvement of the spleen in the chronic infectious or toxic process of rheumatoid arthritis The inhibitory effects of an abnormal spleen are seen at their best in this condition histologically the pleen often shows peculiar arterial vascular lesions which provide but little inkling of the pathological physiology involved The crowding of the marrow with leukocytic cells

and the simultaneous leukopenia are indications that an unusual barrier has been established between the marrow and the blood The return of the blood picture to normal following splenectomy seems to give definite proof to this conception

Gaucher s disease if splenomegaly is present is associated also with well defined leukopenia Although one naturally might consider that this was due to crowding of the marrow with Gaucher cells this is not borne out in the cases in which splenectomy has been performed as shown in the case here reported

Zalmen K a Jewish boy aged 7, had been known to have marked splenomegaly since very early childhood The spleen finally became so large it interfered greatly with his locomotion Petechiae became prominent and numerous ecchymotic areas usually were present The blood showed a moderate degree of normochromic anemia marked leukopenia and moderate thrombocytopenia Biopsy of the sternal marrow showed almost complete occupation by Gaucher cells interspersed amongst which were islands of normal marrow tissue From the biopsy it seemed clear that the pancytopenia was due to myelophthisis rather than to splenic inhibition However splenectomy was decided upon because of the large size of the spleen and the possibility that the hemorrhagic tendency might be improved Following operation there was a dramatic increase in all three blood cell elements, which has been sustained There was furthermore, marked improvement in growth

Boeck s sarcoid at times is associated with very marked splenomegaly if so, leukopenia usually is present When splenectomy is performed, the leukocyte count returns to normal In a recent case of *Hodgkin s disease of the spleen* the presenting problem was marked leukopenia and granulopenia The leukocyte count varied between 800 and 2 000 per cu mm with 5 to 20 per cent of granulocytes Agranulocytosis was considered as the probable diagnosis However, percussion dullness over the splenic area was increased and an x ray of the splenic region revealed splenomegaly Although the spleen was not palpable, it weighed 1 100 gms at the time of splenectomy It showed extensive involvement with typical Hodgkin s disease Following splenectomy there was a gradual rise of the leukocyte count to normal or somewhat higher than normal values The patient later died of Hodgkin s disease following numerous bouts of Pel Ebstein relapsing type of fever

Primary or Idiopathic Splenic Leukopenia — This syndrome was described first by Doan and Wiseman[37] That it is truly idiopathic and not secondary to some as yet unrecognized splenic disorder is not as yet definitely shown However there can be no doubt that there are certain cases ordinarily chronic in which marked leukopenia is outstanding and which are associated with splenomegaly of undetermined origin These cases probably are closely allied to acquired hemolytic anemia of unknown origin and to idiopathic thrombocytopenic

purpura and in fact are associated often with evidences of one or the other or both of these conditions

Doan and Wiseman s first report[3] of these cases was published in a short ab stract in which specific case reports were lacking It was stated that (1) there was no evidence of hepatic di ease ( ) the marrow showed marked leukopoietic hyperplasia and (3) the spleen showed marked leukophagocytosis by clasmato cytes A complete article on the subject with a report of 5 cases was published in 1942[5] One acute case one chronic and three subacute cases were reported In the first three the white blood counts were extremely low between 150 ( ) to 1 800 and with from 10 to 30 per cent neutrophiles In ca es 4 and 5 there was outstanding thrombocytopenia but the leukocytes were only lightly reduced to between 3 500 and 5 000 with from 30 to 50 per cent neutrophiles The sternal marrow in all ca es was hyperplastic with varying degrees of hyperplasia of the red cell white cell or megakaryocytic tissues The spleen was very defi nitely enlarged in 4 ca es and only slightly enlarged in case 4 which in all prob ability was one of thrombopenic purpura with slight leukopenia and lympho cytosis

It is not entirely clear from this series of cases whether they should be com pletely separated as a distinct entity from acquired hemolytic anemia and idio pathic thrombopenic purpura since in both of these syndromes leukopenia not infrequently occurs However as Doan and Wisem in point out the likelihood is present that when the spleen is hyperactive it has effects not only on granulo cyte but on platelets and red cells as well The concept that the spleen produces leukopenia by excessive phagocytosis of leukocytes is open to discussion Cer tainly no very good proof of this has been advanced and the few photomicro graphs bearing on this point leave much to be desired

The same discussion holds true for the spleen in idiopathic thrombopenic pur pura does it engulf and digest platelets or does it act by inhibiting platelet for mation and delivery from bone marrow megakaryocytes? Our studies of the bone marrow before and after splenectomy in this disease indicate that platelet production is inhibited almost immediately following splenectomy there is an enormous production of platelets with a resulting increase in the platelet level in the blood We believe that the same mechanism is present in splenic leuko penia i e splenic inhibition of leukocytic growth or delivery with resultant leuko penia Following splenectomy a release of this inhibition probably occurs with a return of the leukocyte count to normal or leukocytic levels

The spleen in many conditions and particularly when enlarged thus is sub ject to a state which may be called hypersplenism and in which the bone marrow becomes involved This involvement may be selective i e erythroblastic with the development of hemolytic anemia megakaryocytic with development of

thrombopenic purpura or leukocytic with the development of granulocytopenia, or the entire marrow may become involved with varying degrees of anemia, leukopenia or thrombocytopenia, total involvement or pancytopenia Rather than a phagocytic function on the part of the enlarged spleen the evidence seems to point to a great increase in the inhibitory function of the spleen on the marrow with a resultant delay in cellular emission to the blood stream

Miscellaneous Conditions with Leukopenia

EXCESSIVE DESTRUCTION OR ELIMINATION OF WHITE CELLS IN THE TISSUES — In hemolytic anemia there is excessive destruction of red cells either intravascularly or in such tissues as the spleen, the bone marrow meanwhile remaining normal or even hyperactive A similar disorder associated with excessive destruction of leukocytes in the tissues is unknown Nor can much credence be given to the impression that in certain cases of severe sepsis the leukopenia is due to the very rapid elimination of leukocytes from the circulation to an infected locus such as a consolidated lung With extreme leukotactic influences in an infected area and with a normally acting bone marrow the blood stream shows the effects of the very heavy traffic of leukocytes from marrow to tissue, leukocytosis unless the delivery mechanism has become altered, in which case leukopenia occurs

REDISTRIBUTION OF WHITE CELLS FROM THE BLOOD STREAM TO VARIOUS TISSUES — The quick loss of leukocytes from the blood stream and their sequestration in such organs as the liver and spleen probably is more than simply theoretical In traumatic and other types of shock, in the so called hemoclastic crisis following the parenteral introduction of foreign proteins and of toxic products such as snake venom there is often an initial leukopenia which is followed quickly by leukocytosis Lawrence[39] has studied this phenomenon and believes that redistribution leukopenia on the basis of rapid vasomotor changes is of common occurrence This concept had great popularity two or three decades ago when much emphasis was placed upon the effects of the vegetative nervous system on the leukocyte count

LEUKOPENIA OF MISCELLANEOUS CONDITIONS — Thus far leukopenia has been described in relationship to very definite disturbances bone marrow splenic in infections in which attempts at working out physio pathological mechanisms were made There are certain unrelated conditions however in which even speculative mechanisms for the leukopenia are quite obscure Such conditions are the following

Neurasthenia — It has been my experience that many neurasthenic women, whose chief complaint is severe fatigue, have leukocyte counts between 4 000 to

6 000 per cu mm Whether this has to do with diminished muscular activity, excessive flabbiness or other more subtle mechanisms is obscure

Hyperthyroidism — Certain cases particularly very acute ones are associated with leukopenia and with marked monocytosis or lymphocytosis Lymphoid hyperplasia has been noted as a common accompaniment of the disorder and it may be that this phenomenon reciprocal relationship (?) is responsible indirectly for the leukopenia

Various other Endocrine Disorders — Certain cases of hypopituitarism hypoovarianism hypogonadism etc are associated with mild leukopenia of which the mechanisms are quite obscure In hypothyroidism the entire marrow may become somewhat hypoplastic with the gradual development of normochromic anemia leukopenia granulopenia and thrombopenia

Acute Disseminated Lupus Erythematosus Libman Sacks Disease — Leukopenia is common in this disease of unknown etiology and obscure pathology In association with the distinctive rash the prolonged fever the adenopathy and common splenomegaly, the frequent cardiac and renal manifestations and the tendency to involve serous surfaces the leukopenia is of definite diagnostic value Leukocyte counts of 2 000 to 5 000 in association with granulopenia are seen usually There is little if any shift to the left and the lymphocytes and monocytes show no abnormalities The cause of the leukopenia is quite obscure Since anemia and thrombopenia also are present frequently at least two possible mechanisms must be considered a depressed or hypoplastic condition of the marrow and hypersplenism No definite evidence on either of these two possibilities is yet at hand

Boeck s Sarcoid — This disorder which is perhaps infectious in origin and possibly related to tuberculosis is associated usually with leukopenia of from 2 000 to 4 000 per cu mm The characteristic skin lesions may or may not be present, but usually there is generalized lymphadenopathy peculiar pulmonary changes best demonstrated by x ray and frequent splenomegaly The spleen occasionally is extremely large and may represent the only abnormal physical finding In the presence of splenomegaly the nature of the leukopenia is at least partially apparent without splenomegaly the cause of the diminished leukocyte count is obscure although it may be related to the reticuloendothelial hyperplasia within lymphoid tissue (with inhibitory effects on bone marrow?)

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CHAPTER XXII-A

AGRANULOCYTOSIS

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Introduction

Definition — Agranulocytosis is a serious acute disorder of the leukocytes of the bone marrow and blood characterized by severe constitutional manifestations, high fever, sore throat extreme leukopenia and granulocytopenia without other hematologic manifestations such as anemia or thrombopenia, due, at least in many instances, to an allergic sensitivity on the part of bone marrow leukocytes to various drugs, more particularly aminopyrine

Synonyms — The name originally given by Werner Schultz[1] (1922), "agranulocytosis", was criticized early because it might connote a proliferation of 'agranulocytes', i e cells without granules Like many another loose or even incorrect term, such as infectious mononucleosis, pernicious anemia aleukemic

leukemia etc it has managed to survive and to withstand the criticisms of many authors Agranulocytic angina (Friedemann 1923[2]) received wide acceptance for a time particularly in this country With this term the angina sore throat is emphasized a feature which not infrequently is lacking Granulocytopenia (Naegeli 1931[3]) and granulopenia are hardly adequate since a reduction in granulocytes is common in many conditions Malignant neutropenia [4], although it indicates the highly serious character of the disorder suggests a relationship to neoplastic disease furthermore how can a neutropenia be malignant ? Other terms which have been advanced are mucositis necroticans agranulocytica (Weiss 1927), ' agranulocytose pure (Aubertin and Levy, 1928[6]) pernicious leukopenia ' (Fitz Hugh and Comroe 1933[7]) idiopathic neutropenia [8], etc

Schultz[9] in defense of his term agranulocytosis stated in 1933 The term 'agranulocytosis signifies a definite disease characterized by a defect of the granulocytic system It is based on the use of the designation of granulocytes for the granulated cells of the bone marrow and blood Like nephrosis hepatosis etc it signifies a non infectious disease of the granulocyte system He further states, the expression ' agranulocytosis like the Greco Latin expression polynuclear neutrophile and many other hematological terms is a barbarism — but as such it has crept into the literature and become widely used As Plum[10] to whom I am indebted for much data in this article says Much of the criticism of this designation seems somewhat unnecessary at the present time When the nature of the disease its etiology pathogenesis and limitations are settled a more fitting name may perhaps be found instead of agranulocytosis

HISTORICAL

Although it is probably true that accounts of a similar if not identical disease process were made prior to 1922 it is certain that Schultz s paper on Gangranezierende Prozesse und Defekt des Granulozytensystems read before the Berlin Gesellschaft fur Innere Medizin und Kinderheilkunde July 3 1922 was the first in which this disease was definitely described as a new entity and the first to relate the necrotic ulcerations of the mouth and throat with the very low granulocyte count Schultz described 5 cases, all in women which were characterized by deep seated necrotic processes in the mouth and throat extreme leukopenia and granulocytopenia and fatal termination The bone marrow at autopsy showed a reduction in the number of granulocytes of all types Schultz s account was followed quickly by a number of case reports from various parts of the world but more particularly from England the United States and the Scandinavian countries with very few reports emanating from Italy the tropical and

sub tropical countries and the Orient By 1931 when the author s first article[4] on the subject was written, about 200 cases had been reported From 1931 to 1934 inclusive 1,981 deaths were reported from the United States alone[11]

Blood counts did not come into general vogue until about the beginning of the present century As noted in the chapter on Leukopenia infections and other conditions associated with a low white count were considered rare The combination of sore throat and granulocytopenia was reported first by an American, Brown[1] of San Francisco, in 1902 In this case, which is unusually well described for the period agranulocytosis seems probable, although in view of the generalized lymphadenopathy and splenomegaly the possibility of aleukemic lymphatic leukemia cannot be ruled out The patient, a woman of 29 years, became acutely ill with high fever and sore throat The blood findings were hemoglobin 65 per cent red cells 3 240 000, white cells 1 000 polymorphonuclears 1 per cent lymphocytes 99 per cent Just prior to death, which was due to acute edema of the glottis the leukocyte count dropped to 260 per cu mm with 23 per cent granulocytes The case of Schwartz[13] (1904) of a boy aged 9 with 600 leukocytes and a red cell count of 2,000 000 probably was one of " pancytopenia " associated with a severe bone marrow disturbance, probably leukemia Turk[14], one of the outstanding hematologists of his time, in 1907 carefully described the case of a woman aged 45 who showed fever, a generalized embolic (?) eruption of the skin and a leukocyte count of 940 per cu mm with complete lack of granulocytes the red cell count being normal Post mortem examination showed complete lack of normal leukopoiesis in the marrow in the presence of normal erythropoiesis Lymphocytes and plasma cells were common Turk stated there was thus simply a lack of granulocytes, the specific white cell element of the marrow a condition previously completely unknown to me ' That this case was not true agranulocytosis would be difficult to prove, although it must be conceded that the history of 4 weeks illness and the generalized embolic (?) eruption suggest the possibility of acute lupus erythematosus with an unusually low white count

Sturzberg[1] (1912) reported 2 cases with leukopenia of which the first showed lymphatic leukemia at autopsy The second although the leukocyte count was 900 per cu mm and showed complete lack of granulocytes nevertheless was associated with an outspoken hemorrhagic diathesis, thus suggesting a "pancytopenia ' and a generalized bone marrow disorder

Thus, of the various cases described prior to 1922 and which have been cited often as representing typical examples of agranulocytosis only one or two will pass critical appraisal at the present time Doubtless the same criticism holds true for many cases reported since 1922 Is agranulocytosis thus a practically ' new disease appearing like a new planet in 1922, or were cases described

clinically years previously without benefit of leukocyte counts? Pepper[16] attempted to prove that the latter view was correct by having recourse to the older literature of putrid and other types of sore throat but his conclusion from these observations that agranulocytosis was not a new disease can hardly be given serious attention It must be admitted that some factor or factors led to the sudden development of this previously undescribed condition and of these factors probably the most important has to do with the greatly increased use of certain drugs beginning shortly after World War I

The cause of the ' primary disease was quite obscure until Kracke[17] (1931) first suspected and Madison and Squier[18] among others in 1933 first showed conclusively that certain drugs notably aminopyrine were of primary etiological importance The extreme hypersensitivity of certain individuals to aminopyrine was shown not only by Madison and Squier but by a number of other investigators including Benjamin and Biederman[19] Kloster Rohr and Dameshek and *Colmes* Plum s[1] [3] *detailed observations of the blood and sternal bone* marrow following the administration of aminopyrine are of outstanding importance In recent years the introduction and increasing use of the sulfonamide drugs has been attended with the appearance of many new cases

Therapeutically the situation has remained far from satisfactory At first classed as a uniformly fatal disorder later reports up to 1935 indicated that the disease was about 80 to 90 per cent fatal Therapy which was at first non specific and included milk injections x ray treatment etc was modified in 1931 by Reznikoff[24] who suggested adenine sulfate and by Jackson and collaborators [5] (1932) who used a mixture of pentose nucleotides in the attempt to stimulate leukopoiesis in the bone marrow The promise of successful therapeutic results with these drugs has not been completely fulfilled and a similar lack of success has attended the introduction of liver extract yellow bone marrow etc as specific therapeutic agents The use of the sulfonamide drugs for combatting the attendant sepsis was advanced by Dameshek and Wolfson After all death is not due to granulocytopenia per se but to bacterial invasion in a body stripped of its normal leukocytic defense

Etiological Factors

Thoughts regarding the etiology of agranulocytosis have undergone drastic change since the disease was first described Originally considered as a peculiar infectious di ease with outstanding leukopenia and later thought to have allergic or endocrine relationships its close connection with certain chemicals soon was recognized by a number of observers The extraordinary hypersensitivity in certain individuals of the bone marrow leukocytes to drugs such as aminopyrine was soon demonstrated

Infections

Schultz[1] in his first description of the disease stated "that one was dealing with a peculiar infection with a fundamental bone marrow disturbance of the granulocyte series' This concept was only natural since there can be no question that the constitutional symptoms are those of a severe infection with or without bacteremia What is more a number of infections may be associated with leukopenia often of marked degree This is particularly true of certain cases of fulminating streptococcic sepsis in which unusually severe constitutional symptoms are associated with a dropping white count However, as already pointed out the differential count in these cases despite the leukopenia, shows a marked increase in granulocytes with the presence of many immature forms

What was long unrecognized was that the infection was a phenomenon, which was simply secondary to complete lack of the granulocyte defense system The finding of various types of organisms in blood and post mortem cultures was partly responsible for this error Stewart Tocantins and Jones [7] analyzed 59 cases in which post mortem cultures were obtained Positive cultures were obtained in 36 cases streptococci 15 cases *B coli* 10 cases, staphylococci 6 *B pyocyaneus* 6 pneumococci 4 and other organisms in 8 cases It is to be noted that of the 36 cases with post mortem positive cultures only 11 showed positive cultures before death Plum[10] studied 13 cases finding streptococcus hemolyticus in 7, a non hemolytic streptococcus in 1 *B coli* in 4, staphylococcus aureus in 3, *B proteus* in 3 and pneumococcus in 2 Thus 20 organisms were isolated from 13 cases indicating mixed infections in several instances By the very careful techniques used a positive culture was demonstrated in every instance of the disease Control observations in individuals dying of both infectious and miscellaneous diseases demonstrated decidedly less infection than in the cases of agranulocytosis The finding of various types of infectious organisms mixed infections frequently being present and the complete lack of any epidemiological connection from patient to patient are all indicative of the secondary nature of the infection and point to a more fundamental condition

Endocrine Disturbances

That at least certain cases of agranulocytosis have a dysfunction of the endocrine system was seriously considered by a number of observers just prior to the time of acceptance of drugs as the chief etiological factor in the disease Since the great majority of the cases occur in women it was natural to suspect the menstrual cycle of having some causal relationship W P Thompson [8] (1934) analyzed 25 cases of agranulocytosis occurring in women within the menstru

ating age Of these 7 were either sterile or not menstruating for various reasons Of the remaining 18 17 entered the ho pital with agranulocytosis while menstruating and had developed their first subjective symptoms at the beginning of the period Relapses occurred in 6 cases and on each occasion simultaneously with the appearance of the menstrual cycle

Jackson and Merrill [9] and Stephens and Lawrence[3] reported individual cases in which a marked *cyclic neutropenia* was present in association with the menstrual cycle The former observers postulated an ovarian disturbance with effects on the bone marrow leukocytes In the case of Stephens and Lawrence bilateral oophorectomy failed to alter the course of the disease which improved only after all types of analgesic drugs were discontinued A similar cyclical case was reported by Dameshek and Colmes in this patient too bilateral oophorectomy together with hysterectomy had been performed previously it was only when aminopyrine was supected as a cause and completely discontinued that the cycles of neutropenia ceased

Thus the clinical descriptions of even the most outstanding cases in the literature in which an endocrine etiology is postulated are for the most part defective in that a drug etiology was either not suspected or insufficiently inquired into or simply ignored as probably of no importance It is more than likely that the cyclical neutropenia of many cases as in Thompson s series and in the cases of Jackson and Merrill and of Stephens and Lawrence was induced not by hormonal changes but by various analgesics taken just prior to or at the onset of the catamenia The tendency of many women to use such widely heralded drugs as midol *which until recently contained aminopyrine is well known*

The menstrual theory is invalidated further by the appearance of many cases in the older age group Plum found that agranulocytosis was most frequent between the ages of 55 to 65 and not in the ages at or about the menopause No relationship to the pituitary adrenal thyroid or pancreas has been commented upon nor has the pleen been incriminated in true cases of agranulocytosis One must therefore dismiss the endocrine system as almost certainly without relationship to the disease

Allergic Disease

It was recognized early that many patients with the disease previously had had asthma hay fever and other conditions in which hypersensitivity played a dominant role Kammerer[31] (1929) likened the disease to protein shock with leukopenia Pepper (1931) stated quite definitely agranulocytic angina may have allergy as the background not of the angina directly but of the leukopenia which permits the angina As with the other etiological factors enumerated above the allergic concept was abandoned when the unique importance of chemi

cals as etiological agents was recognized That an allergic or hypersensitive manifestation was, however, present in association with the chemical or drug factor shortly was seen clinically and reproduced experimentally in recovered patients

Chemicals and Drugs

Although the leukopenia following the use of such chemicals as benzol, arsenic arsphenamine, neoarsphenamine, gold, radium and radio active substances had been described for a number of years, its relationship to typical agranulocytosis was not seriously entertained at first This probably was because the reduction in total leukocytes and in granulocytes was slight as compared with agranulocytosis, the severe constitutional symptoms with acute onset usually were lacking, there was almost always associated anemia or thrombopenia indicating total bone marrow disease the recovery rate was much higher, about 70 per cent as compared with 10 to 20 per cent with agranulocytosis For a number of years in fact a chemical etiology for the latter disease was not even suspected Kracke[17 33] (1931–1932) must be given credit for putting together a group of apparently unrelated facts and deducing from them that certain chemicals or drugs probably were the fundamental cause of the disease He said 'The observation that the disease occurs largely in Germany and the United States, that it occurs in middle aged white women for the most part in women of leisure or women living under good economic conditions, that it is seldom seen in the negro, that most of the patients have a history of previous medical care or treatment with various drugs that the coal tar series of drugs has its widest range in those parts of the world in which the disease is most frequent that these drugs and chemicals contain the altered or modified benzene ring, and that benzene is the one outstanding leukocyte depressant, lead me to believe that this substance or its products must be seriously considered as the cause of this condition A thorough consideration of the nine cases of agranulocytosis that I have studied reveals the fact that eight of the patients had been taking drugs of the coal tar derivatives prior to the clinical onset The drugs used were phenacetine amidopyrine peralga and dial, four proprietary preparations that had been administered in large quantities to four patients later developing agranulocytosis" Kracke[17 33] and Kracke and Parker[34] believed that benzene, particularly in combination with nitrogen or the amino (NH_2) group, was responsible for a direct toxic action on the bone marrow For the more complex drugs such as amidopyrine or phenacetine they postulated, chiefly on a priori grounds, an 'atypical oxidation in the gastrointestinal tract with the formation of catechol quinones or hydroquinones

In 1933 a number of completely independent observations were made by

Videbeck[35] of Denmark, Stenbeck[36] of Sweden Costen[37] of the United States de Vries[38] of Holland and Madison and Squier [9] of the United States in all of which a chemical or drug etiology was strongly suspected Madison and Squier were the first to point the finger squarely at amidopyrine as the most probable cause of the disease and to make the observation of recurrence in 2 patients who had again taken the drug after having recovered from a previous attack Shortly thereafter Holten Nulsen and Transbøl[39] of Denmark reported 5 cases of agranulocytosis which followed the use of ordinary doses of amidopyrine for the relief of pain and discomfort of various medical conditions Numerous reports implicating amidopyrine more recently designated as aminopyrine which is the U S P official name shortly appeared chiefly in the Scandinavian countries and in the United States

Aminopyrine — Through a large number of case reports more than 200 aminopyrine was recognized quickly as the most important single etiological factor in the disease although a number of observers chiefly German made light of this contention and pointed to the " harmlessness of pyramidon and its great value as an anodyne and antispasmodic Kracke and Parker[3] stated that the disease was about 8 times as frequent in the medical group including physicians their families nurses dentists hospital employees etc who had access to and commonly sampled the many newer pain relieving remedies Most of these contained aminopyrine often hidden under a euphonious pseudonym A partial list of American proprietary preparations that did or do contain aminopyrine was published in Kracke s text book of hematology (May 1935) from information supplied by the Council on Pharmacy and Chemistry American Medical Association A number of these products such as allonal and midol since then have modified their formulae to exclude amidopyrine On the other hand such newer preparations as causalin have arisen to take their place There are furthermore a number of patent medicines and medicines with secret formulae for tonics pain killers etc which contain aminopyrine often under a disguised name Many patients questioned about previous use of drugs fail to remember particularly when severely ill of the previous use of some drugstore remedy Other patients apparently are ashamed to divulge this information and in a few cases known to the writer information was withheld deliberately by the physician in charge of the case The many cases in the literature in which no drug etiology was found on these accounts must be questioned seriously

Plum[10] studied this question very carefully From 1923 to 193 prior to knowledge regarding the important role of amidopyrine in only 13 of 32 cases was there a history of either the definite or probable intake of amidopyrine On the other hand from 1933 to 1936 of 56 patients seen 48 definitely had taken amidopyrine and 4 probably had taken the drug 52 in all In only one ca e

was there definitely no intake of amidopyrine In the majority of the cases the last dose of the drug was taken shortly before the onset of the disease Since the total dosage used usually was small, and since in several cases it was known with certainty that amidopyrine had been used previously without reaction the possibility of the development of hypersensitivity was suspected

Aminopyrine Hypersensitivity That patients developing agranulocytosis might be unusually hypersensitive to a given medication, notably aminopyrine, was suggested by the relatively few cases of the disease seen among the many thousands of users of the drug As Dameshek and Colmes pointed out from a rough survey of prescription administrations as compared to cases of agranulocytosis, only about 1 case develops with the use of 10 000 prescriptions Watkins[41] stated that there was a definite possibility of idiosyncrasy to the drug and Hoffmann, Butt and Hickey[4] suggested a possible individual susceptibility in the nature of an allergic reaction Groen and Gelderman[43] also considered an idiosyncrasy and pointed to the above mentioned case of de Vries, in which a few hundred milligrams of pyramidon regularly caused chill and granulopenia Definite hypersensitivity was demonstrated first by Madison and Squier[18] in a physician who had recovered from three previous attacks each following the use of amidopyrine Ten months after the last attack the patient was deliberately given 0 3 gm (gr 5) amidopyrine by mouth Within three hours the temperature rose to 10 ° F, and the patient complained of vague muscular pains and malaise Within twelve hours the leukocyte count had dropped from 7 800 to 2,000 per cu mm and the granulocytes from 4,750 to 250 Subsequently there was a gradual rise A similar experiment was performed on another patient Benjamin and Biederman[19] (1934) reported a similar experiment in a nurse who had had several previous attacks of leukopenia all of them preceded by the use of various proprietary preparations Three years after the last attack she was given 0 65 gm (gr 10) of amidopyrine by mouth Within three hours the white cell count had fallen from 3,700 to 1 700 with a corresponding reduction in granulocytes within 24 hours the leukocyte count was 1 000 per cu mm The use of aspirin and of isopropylbarbituric acid was without effect on her leukocyte count Benjamin and Biederman attempted to define more accurately the nature of this hypersensitivity Since patch tests intracutaneous tests and passive transfer tests in their patient all were negative, they concluded that the reaction was not atopic but more in the nature of a drug hypersensitivity with the hemopoietic system acting as a shock organ

Dameshek and Colmes (1936) studied the question further in 4 recovered cases of aminopyrine agranulocytosis One patient reacted strikingly within 90 minutes after the oral administration of 0 6 gm (gr 10) of aminopyrine developing in quick succession severe headache, nausea, marked flushing of the face,

malaise, vague joint pains and weakness Following another dose the headache became intensified Thirty six hours after administration of the drug there was extreme weakness and prostration, and the leukocyte count had dropped from a normal value of 9 000 to 1 400 per cu mm with 2 per cent granulocytes Subsequently there was complete lack of granulocytes at which time numerous necrotic ulcerations were noted on the tongue and lips Two patients developed moderate clinical and leukopenic reactions The skin reactions to various scratch tests patch tests passive transfer tests and intradermal tests with the drug alone were essentially negative in all four patients Two of 3 patients shortly after the intradermal administration of amidopyrine for skin testing developed all of the clinical and hematological features of agranulocytosis although the total quantity of drug used did not exceed 10 mgm (gr $\frac{1}{6}$)

Following the principle of Horsfall[44] who studied formaldehyde sensitivity, and who found that a combination of the chemical with blood serum gave positive intradermal results whereas solutions of formaldehyde in water gave negative readings Dameshek and Colmes prepared mixtures of 5 per cent aminopyrine solution with varying quantities of human blood serum which then were aged in the refrigerator for several days When intradermal tests then were done with this serumized aminopyrine strongly positive reactions developed suggesting a possible drug protein linkage as the basis of the allergic or hypersensitive reaction

Plum[10, 3] (1934–1937) studied the reaction of the blood and sternal bone marrow before and after the administration of aminopyrine in 7 recovered cases of agranulocytosis The rapid development of changes in the bone marrow granulocytes (see discussion of physiopathological mechanisms) followed by the hematological and clinical changes were described carefully

These and other studies demonstrated conclusively the extreme hypersensitivity of certain individuals to aminopyrine The production of agranulocytosis shortly after the intradermal introduction of only a few milligrams of the drug tended to disprove the theory of Kracke and Parker[34] regarding intestinal oxidation and resultant toxicity Whether or not this hypersensitivity on the part of some individuals should be considered as an allergic atopic or anaphylactic state or as a simple idiosyncrasy to a drug has remained obscure perhaps because the exact differentiation between these terms in itself is obscure

Sulfonamide Drugs —The well nigh miraculous effects of the sulfonamide drugs in the control and cure of the various pyogenic infectious states unfortunately have not been an unmitigated blessing since reactions sometimes fatal have occurred not infrequently Undoubtedly the most serious of these is agranulocytosis since usually it is fatal That these drugs occasionally might affect white cell production was suspected quickly from their chemical structure, which showed not only a benzene ring but NH groupings This was reminiscent of

the "benzamine etiology, which Kracke earlier had postulated as the most probable cause of agranulocytosis As the various sulfonamide drugs have been introduced, they have each been followed by case reports of various reactions, including severe leukopenia and agranulocytosis

Long and Bliss[4] pointed out that there is no direct effect on the white cells as such Of 408 cases, which were given sulfanilamide and studied at the Johns Hopkins Hospital, none exhibited significant changes in the white cells which could be attributed to the toxic effects of the drugs This and the other sulfonamide drugs appear to have their therapeutic activity not through the leukocytes but by means of a direct bacteriostatic effect However, there can be no doubt that while the drug is circulating various organs, including the marrow, may become involved

Sulfanilamide The incidence of severe neutropenia or frank agranulocytosis is very low Long and Bliss found 2 cases among 408 treated, approximately 0 3 per cent Goodman and Gilman[46] report an incidence of 0 3 per cent of leukopenia with granulocytopenia and 0 1 per cent of acute granulocytopenia agranulocytosis In the great majority of the cases agranulocytosis appeared only after the drug had been administered for 17 days or longer, and only after 40 to 50 gm had been given Cases occurring within a few days after the first administration of the drug are rare but on the other hand a number of cases have been reported in which relatively small doses were given for a few days the drug stopped and then resumed again Thus, Berg and Holtzman[47] report the case of a man under treatment for gonorrhea with 10 gr (0 6 gm) doses every 4 hours The development of slight fever cramps gaseous eructations and nausea forced the discontinuance of the drug, which was resumed, discontinued and resumed again at 5–7 day intervals Finally the patient developed a chill fever and agranulocytosis and died Jones and Miller[48] report a similar case also under treatment for gonorrhea Each administration of the drug was followed by fever In this case the lowest leukocyte count was 2,300 with 5 per cent granulocytes, and the patient recovered This half hearted administration, cessation and re administration of small doses of the drug for such questionable indications as sore throat grippe a sinus attack etc probably have been responsible for many cases many of which undoubtedly have not been reported In many of these cases a febrile response has occurred with each re administration this should therefore, be a warning signal of possible severe neutropenia

That the drug may be a cumulative poison in many cases is suggested not only by the late development of agranulocytosis but by its occasional occurrence 3 to 4 days after the drug has been discontinued However, even though the severe reaction of agranulocytosis does not develop until the drug has been given persistently and in large dosage for at least 2 weeks it is highly probable that some

form of hypersensitivity nevertheless plays a role since of the hundreds of cases given similar dosages over a similar period of time only a few develop the leukopenic condition The reaction of hypersensitivity is brought out unusually well in those cases which have been given mall doses of the drug intermittently Here the body tissues more particularly the leukopoietic cells of the bone marrow probably have the opportunity of developing an allergy to the drug with the result that with the second or third administration agranulocytosis may develop

Long and Bliss reported one case in a boy with hemolytic streptococcal mastoiditis and clinical adenitis in which a sharp drop in the white cell count and neutrophiles developed following each attempt to establish sulfanilamide therapy Several observers have however tried to reproduce leukopenia by re administration of the drug to recovered cases but almost always without success However, in the recovered case of McGuire and McGuire in which agranulocytosis white cells 450 per cu mm had developed 2 months previously the leukocyte count was observed carefully after 0 5 gm (gr 7½) of sulfanilamide was administered After 5 days there was a fall in granulocytes from the initial value of 82 per cent of 13 050 (10 701) per cu mm to 35 per cent of 9 250 (2 737) per cu mm The development of fever as a premonitory sign of granulopenia has been emphasized by many observers and suggests that the drug hould be discontinued immediately if this develops and is presumed to be due to the drug Various other types of tests for hypersensitivity including the serumized drug test as developed by Dameshek and Colmes for aminopyrine have been tried but without success The exact mechanisms for the development of agranulocytosis with sulfanilamide must therefore be considered obsure although a hypersensitivity phenomenon probably is fundamental in both the large dose and small dose cases Direct injury to the leukopoietic tissue of the bone marrow without actual hypersensitivity is however possible in those cases given large doses over a period longer than 2 weeks Several authors have emphasized the obvious fact that it is almost never wise to continue the drug longer than 7 to 10 days since if its maximum effect has not been obtained by that time it almost certainly will not be obtained later Whatever the mechanisms however it is universally agreed that complete agranulocytosis developing during sulfanilamide therapy carries with it a very poor prognosis

Sulfapyridine Goodman and Gilman[45] report an incidence of severe leukopenia with granulocytopenia in 0 6 per cent of the cases and of agranulocytosis in 0 3 per cent Delgopol and Hobart[9] found 2 cases of leukopenia and 2 of severe granulocytopenia among 35 cases given sulfapyridine for pneumonia Blake and Haviland[1] observed 4 instances of granulocytopenia in 128 cases of pneumonia treated with sulfapyridine The same considerations as with sulfanilamide regarding long continued and interrupted dosage apply to sulfapyridine

Thus of 30 cases of sulfapyridine agranulocytosis analyzed by Goldman and associates 39 per cent had taken the drug for 10 or more days, agranulocytosis developed most commonly between the 17th and 25th day of administration In 43 per cent of the cases interrupted administration had been employed, and severe granulopenia developed on resumption of the drug The remaining cases 18 per cent, developed early in the administration of the drug, although the drug never had been given previously

Sulfathiazole Goodman and Gilman[46] report an incidence of mild leukopenia with granulocytopenia in 1 6 per cent of administrations Agranulocytosis as such did not occur in the combined reports of Long and associates, Flippin and co workers [3] and Blake and Sadusk [4] However a few typical cases all fatal were reported later In the case of Kennedy and Finland[55] agranulocytosis developed during the third week of treatment for subacute bacterial endocarditis, when a total dosage of 125 gm of the drug had been given Jackson[56] reported a fatal case in which interrupted dosage for gonorrhea had been utilized in this instance agranulocytosis developed, although a total of only 15 gm of the drug had been given

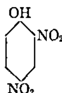
Although similar considerations regarding the length of administration of large dosage and the matter of interrupted dosage are applicable to sulfathiazole as to the other sulfonamide drugs it is possible that the incidence of granulopenic reactions is smaller The development of rash or fever, drug fever are significant warning signs of possible impending granulocytopenia Too long an administration of drug except when the dangers are fully assessed beforehand, as in subacute bacterial endocarditis should be avoided

Sulfadiazine This drug appears to have fewer toxic effects than the related compounds However that typical agranulocytosis can occur has been reported[59] The rapid development of high drug concentrations in the blood and the relative freedom from such unpleasant side effects as nausea and anorexia have popularized the use of this drug as against sulfathiazole This in some ways is unfortunate, since many patients probably are given the drug unnecessarily and over a longer period of time than is actually required This may well result in many, as yet unreported cases of agranulocytosis In some recent animal experiments[53] the continued administration of sulfadiazine in guinea pigs was followed frequently by progressive leukopenia, granulocytopenia and death, whereas sulfathiazole in the same dosage apparently failed to lower the leukocyte count This may be due to the higher concentration of sulfonamide which is obtained with sulfadiazine Recent observations suggest that the various sulfonamide drugs act in much the same way, with minor variations as to side effects and that the supposed differences are merely a matter of the concentration of drug which has developed in the circulating blood and tissues

General Comments on Sulfonamides The sulfonamide drugs all must be considered as double edged swords Potent therapeutic agents as they undoubtedly are they carry with them the potential threat of serious involvement of the blood forming apparatus Thus they should be given only if specifically indicated and for as short a time as possible Vigorous efforts should be made to guard against the development of hypersensitivity (This matter will be considered at greater length in the section on Prophylaxis) However although these drugs may be productive of leukopenia and granulocytopenia they should never be denied to a patient who has a pyogenic infection and simultaneously shows leukopenia or even agranulocytosis Thus it was noted early that the severe leukopenia of certain cases of streptococcic sepsis or pneumonia was no deterrent to sulfonamide therapy and that excellent therapeutic results could be obtained in these cases[1] In fact leukocytosis usually develops when the sulfonamide drug is given More recently Dameshek and Wolfson stated that death in aminopyrine agranulocytosis ordinarily is due not to the lack of granulocytes per se but to the accompanying sepsis With this in mind and with the knowledge that the drug acted as a bacteriostatic agent without reference to the leukocytes sulfathiazole was used in 2 cases as a therapeutic agent despite the complete lack of granulocytes The response in each case was completely favorable Since this report other similar cases have responded favorably to treatment The presence of severe granulocytopenia in Hodgkin s disease the various types of leukemia and in various conditions of pancytopenia in which the granulocytes are greatly reduced also is no deterrent to the use of the sulfonamide drugs which even under these conditions can be expected to have their typical therapeutic effects Thus although granulocytopenia may develop following the use of the sulfonamide drugs their use in sepsis with leukopenia in various pancytopenic conditions associated with leukopenia and secondary sepsis and in aminopyrine and other types of agranulocytosis with secondary sepsis is logical and often effective

An important and often difficult problem which not infrequently arises during the administration of the sulfonamide drugs is the development of leukopenia Is this due to the sepsis or to the drug? If to the latter should the drug be discontinued? The answers to these questions may be very difficult and may require the utmost in the physician s judgment and in his knowledge of the action of the sulfonamide drugs as well as of the changing blood pictures in sepsis These matters will be discussed in greater detail under Differential Diagnosis Suffice it to say here that if the physician is convinced that sepsis is spreading or is still present the drug should be continued albeit perhaps in smaller dosage Another possibility is to shift the type of sulfonamide since if hypersensitivity is due to one chemical a similar hypersensitivity even to a closely related chemical is not necessarily present

Dinitrophenol — This chemical, 2 4 dinitrophenol, has the following structural formula



Closely related to the explosive trinitrotoluol ("T N T"), it first received attention in munitions workers during World War I as a cause of excessive stimulation and weight loss[59] Upon later investigation it was found to cause hypermetabolism and was thus introduced in 1933 into clinical medicine as a weight reducing agent[60] It received quick popularity and became the chief ingredient of a number of weight reducing nostrums Toxic effects soon were noticeable irreversible hypermetabolism with death, various types of skin lesions late cataract formation, hepatitis, anemia, thrombopenia and extreme neutropenia Dameshek and Gargill[61] (1934) reported 2 cases one fatal, of dinitrophenol agranulocytosis In he first case 200 mgm daily and later 300 mgm daily had been used for six weeks The patient died with a white count of 100 per cu mm and with no granulocytes In the second case doses of 130 195 and later, 325 mgm were given daily for about 7 months, following which fever, disturbances in the gums and throat and extreme leukopenia and granulopenia developed The leukocyte count was 875 per cu mm with complete absence of granulocytes Recovery occurred after the administration of large doses of adenine sulfate

The mechanism of the toxic effects of the drug has never been definitely established The occurrence of urticaria and angioneurotic edema in certain individuals and the marked individual variability in tolerance of the drug both suggested a reaction of hypersensitivity or allergy This was also brought out by the relatively few cases of agranulocytosis reported among the many thousands of individuals who had used the drug It should be stated, however, that many cases probably for various reasons were not reported Thus Dr R R Kracke[8] in 1934 was told of 16 unreported cases while presenting his exhibit at the American Medical Association meeting of that year

Like the sulfonamides the drug probably acts in some cases as a cumulative poison on the bone marrow and in others causes hypersensitivity due to interrupted administration That the 'benzamine' grouping which Kracke postulated, was important in the development of agranulocytosis is well borne out in the chemical formula of this drug Fortunately, as the numerous serious toxic reactions induced by dinitrophenol soon became apparent, its use by physicians was discontinued quickly However its presence as an ingredient of a number of nostrums still is possible, especially in outlying districts The possibility that a weight reducing drug has been used should, therefore, be investigated in any obscure case of agranulocytosis

Other Drugs — In 1938 Fitz Hugh[63] listed the following drugs which were

suspected or proved in their relationship to agranulocytosis: aminopyrine, dinitrophenol, arsphenamine, neoarsphenamine, neostibosan, acetphenetidin, novaldin, causalin, quinine, cinchophen, nirvanol, plasmochin and the sulfonamide drugs. He might also have added benzol, radium and radioactive materials such as thorium and mesothorium, all of which have a powerful effect on the blood forming organs.

The *barbiturates* have been suspected many times but rarely has there been clear-cut proof of their relationship to the disease. In fact, their connection with the disease usually is doubted[33]. In Watkins' series of 53 cases (1934) 17 developed agranulocytosis after the use of barbituric acid preparations without the simultaneous use of aminopyrine. In two recovered cases typical agranulocytosis developed following the administration of test doses of 0.4 gm. of sodium amytal and 0.1 gm. of amytal respectively. Alurate (allyl isopropyl barbituric acid) seems to have been definitely incriminated in a case reported by Hadler[34] in which a test dose given upon the patient's recovery initiated marked granulocytopenia. It is of interest that this drug is closely related to sedormid (allyl isopropyl acetyl carbamide) which has resulted in many instances of thrombocytopenia[7]. Aside, however, from these few well defined cases, it may be stated that the barbiturates have little if any relationship to agranulocytosis.

Novaldin and *causalin*, which are closely related to aminopyrine, both have been incriminated as etiological factors in cases of agranulocytosis. Novaldin[1], which has been given occasionally as a substitute for aminopyrine, is almost the same drug with the exception that one of the CH_3 groups is replaced by CH_2SO_3Na. Causalin[2] contains approximately equal parts of aminopyrine and hydroxyquinoline; it has been a fairly frequent cause of agranulocytosis in recent years. Recommended as a cure for arthritis, and usually with the picture of a stooping crippled man on the box cover, it has often duped the unwary and even those better informed individuals who might have heard of the dangers of aminopyrine. Jackson[6] reported some of the first cases in 1938.

Antipyrine (phenyl dimethyl pyrazolon) has been reported only once[4]; acetanilid[10] ($C_6H_5NHCOCH_3$), phenacetin[4] ($C_6H_4\langle^{OC_2H_5}_{NHCOCH_3}$), cinchophen (phenyl quinoline carbonic acid) only rarely. It cannot be said that a definite relationship of these drugs to agranulocytosis has been proved.

Quinine, a methyl compound of cuprein, one of the alkaloids of cinchona bark, has been incriminated as a cause of agranulocytosis in a few apparently clear-cut cases as cited by Plum[1]. Plasmochin (dimethyl amino isopentyl amino-oxyquinolin), which is used in the treatment of chronic malaria, may precipitate the disorder also (Plum).

Metallic drugs such as gold, radium, radio active substances, arsenic, arsphenamine, neoarsphenamine and bismuth all have been cited as causes of agranu-

locytosis However, in contrast to aminopyrine, which has characteristic effects solely on the leukopoietic tissue of the marrow, these metallic drugs may involve either the entire marrow, panmyelopathy, or various combinations of these elements Thus, there may be total or "selective" involvement Plum[10] has reviewed the various cases to 1937 of leukopenia, granulocytopenia and sore throat without anemia or hemorrhagic diathesis occurring after treatment with arsphenamine (salvarsan) and neoarsphenamine He points out that, although they resemble pure agranulocytosis, they differ from it in several particulars as lower age incidence higher incidence of males higher leukocyte count which was under 1,000 in only 3 or 14 cases, eosinophilia not present in the "pure" form of the disease, much lower mortality rate, 30 per cent as against 70 to 90 per cent, the appearance of sore throat prior to the greatest decline of leukocytes whereas in aminopyrine agranulocytosis there is disappearance of granulocytes first and sore throat second Of 47 cases of salvarsan leukopenia only 14 were not associated with either anemia or thrombopenia

Physiopathological Mechanisms

From the various experimental investigations, particularly with aminopyrine, and from the large clinical and pathological material at hand it is possible to piece together the various steps in the evolution of the disorder of agranulocytosis These may be grouped as follows (1) sensitization, (2) granulopoietic "shock", the bone marrow leukopoietic tissue acting as the shock organ, (3) disappearance of granulocytes from the circulating blood and tissues, (4) loss of the body's first line of defense against the bacteria normally present in such areas as the mouth, throat etc, (5) development of necrotic areas and localized infection (6) bacteremia with chills and fever and finally (7) overwhelming sepsis and usually, death

Sensitization apparently occurs in only a few individuals, perhaps in only 1 among 10 000 taking the drug The exact mode of sensitization is not known although the experiments of Dameshek and Colmes suggest a drug serum combination acting as an antigen with the development of an antibody It has not been possible however, to demonstrate such an antibody either by direct test or by the use of the Prausnitz Kuster phenomenon As with the pollen of ragweed hay fever, sensitization may occur shortly after the first contact or only after several years of contact Many cases of agranulocytosis are seen in which the patient took aminopyrine for years with impunity but then developed typical agranulocytosis after only 10 to 15 grains of the drug In all probability there are various collaborative factors which assist in the development of the sensitization

That sensitization is at the bottom of most cases can hardly be denied from the evidence brought out in recovered cases Many observers have shown that 5 to 10 grains of aminopyrine will result in typical hematological and clinical effects in individuals who have recovered from an attack and who give a history of the previous use of aminopyrine Colmes and I demonstrated in such cases that the intradermal administration of less than 10 mgm of the serumized drug resulted in typical agranulocytosis

The sensitization in all probability affects to some extent the entire body although the leukopoietic tissue of the bone marrow is involved chiefly Thus most of the individuals tested showed severe headache malaise sharp rise in fever and vague bone pains This is reminiscent of the drug fever which often is present as a premonitory feature of sulfonamide granulopenic conditions

That the bone marrow is directly or toxically injured by such tiny doses as 10 mgm of aminopyrine is unlikely more probable is the development of a shock phenomenon with sudden arrest of granulocyte production in the marrow A more direct toxic action cannot however be denied especially in the sulfonamide cases in which the drug has been given continuously and in large dosage for a period of 7 days or longer before the appearance of any of the early evidences of agranulocytosis

Fitz Hugh and Krumbhaar[73] first used the designation of maturation arrest to describe the condition of the marrow in the disease These observers found in several instances that the marrow was either normally cellular or even hypercellular There was however, a great relative increase in the immature forms with an apparent lack of maturation towards mature granulocytes the latter frequently were lacking However many reports are at variance with the findings of Fitz Hugh and Krumbhaar These discrepancies probably are due to observation of the marrow at different times in the course of the disease and under varying conditions of severity

Ilum s carefully conceived experiments[1,4] in which the bone marrow and blood were studied simultaneously in recovered cases following the administration of aminopyrine showed quite clearly that the immature granulocytes myeloblasts promyelocytes myelocytes and metamyelocytes gradually diminished in the course of a few days coincidentally followed by a relative increase in mature granulocytes With continuance of the process in the more severe cases the mature granulocytes gradually became completely depleted and finally in the very severe and fatal non experimental cases the marrow became hypocellular These experiments showed not a maturation arrest but rather a very definite decrease of the early granulocytes The reaction of hypersensitivity on the part of the marrow acting as a shock organ nus seemed to be centered on the granulocyte precursors and only eventually on the mature granulocytes The stock of

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Pathology

Bone Marrow

The most important tissue affected in agranulocytosis is the one which has until recent years been least studied by pathologists the bone marrow Until the last decade or so most pathologists were content to dismiss their descriptions of the marrow with a brief statement as to its gross appearance when the femur was opened it was yellow gelatinous deep red purplish etc Gross descriptions are however, of but little value since a red marrow may be normal hyperplastic, congested with blood or hemorrhagic A yellow marrow is truly inactive but may nevertheless show foci of malignant or leukemic cells or the end stages of a Hodgkin s granulomatous process

Careful histological examinations of the marrow have been made frequently in the last decade or so and prior to that only by occasional pathologists who were convinced that the findings in the marrow were connected quite closely with the blood picture and that it was possible to obtain some information from its study Many observers who were appalled at first by the apparent complexity of a tissue which was occupied by such a diversity of cell types have learned without too much difficulty that the marrow ordinarily contains 3 outstanding and readily recognizable cell types nucleated red cells granulocytes and megakaryocytes All of these show varying degrees of maturation which unfortunately is not too well brought out in fixed tissue sections The insistence by numerous hematologists that smears made directly by imprint from bits of marrow or obtained by sternal puncture are far better for histological study than marrow sections which have gone through various fixing and shrinking agents finally is proving effective Sections are important in studying topography for study of the fine cellular histology smears made like blood smears and stained with Wright s or Giemsa s stain are unexcelled[7]

The histology of the marrow in individuals dying of agranulocytosis is variable This variability probably is explainable on the conditions under which the patient dies The immediate reaction to the shock of hypersensitivity to aminopyrine or other drug is a reduction in granulocyte precursors which shortly is followed by a loss of mature granulocytes This leaves the marrow with practically no granulocytes mature or immature With a patient dying at this stage usually of overwhelming sepsis the marrow may show normal erythroblastic islands with their normal maturation from erythrogones to mature normoblasts normal megakaryocytes but complete or almost complete absence of granulocytes Other leukocytic cells which under normal circumstances are present in small numbers and barely visible among the large numbers of other white cells may now become

mature granulocytes in the marrow having thus become depleted with no new cells being formed the blood inevitably became depleted of granulocytes

The most marked reduction of granulocytes in the cases of Dameshek and Colmes occurred 12 hours 2½ days 7 days and approximately 2 weeks respectively after the administration of aminopyrine In the cases of Plum a similar variation was noted, the lowest granulocyte counts being obtained at 1 1 2 4, 7, 11 12 and 18 days respectively after administration of the last doses of aminopyrine Plum found an initial shift to the left in the morphology of the polymorphonuclear leukocytes with the appearance of many immature polymorphonuclears, soon followed by the presence of only mature polymorphonuclears and finally their complete disappearance, leaving only lymphocytes and a varying number of monocytes in the circulating blood

Disappearance of the granulocytes from the blood and from the tissues as well is the fundamental and outstanding feature of the disease, since upon this phenomenon depends the clinical course It had been assumed earlier that infection came first and reduction in granulocytes second This is the reverse of the actual situation

The lack of granulocytes in the tissues allows the normal organisms, so prevalent in the mouth, throat, vagina, rectum etc to flourish without hindrance The disappearance of granulocytes results in loss of the body's first and perhaps most potent line of defense against invading organisms

It is apparent that the polymorphonuclear cells have a constant and continuous function to perform in destroying or at least neutralizing potentially dangerous organisms for as soon as the granulocyte defenses are depleted numerous infections appear in areas of greatest bacterial contamination as in the throat the mouth the gingivae the rectum, etc

Ordinarily the appearance of a break in the body's defenses say in the area of a tonsil or the peritonsillar space is followed by the streaming in of large numbers of granulocytes with localization of the process in one area In the absence of granulocytes, however, no such localization takes place An area of necrosis develops and shortly following it there are marked constitutional symptoms such as chills and fever suggesting bacterial invasion of the blood stream The body then may become flooded quickly with various types of invading organisms as post mortem bacteriological culture studies have shown Thus the final stage of clinical agranulocytosis is overwhelming sepsis due to unopposed bacterial invasion in a body stripped of its granulocyte defenses Thus death is due not to the fundamental feature of the disease the agranulocytosis but to the sepsis, which is a direct consequence of the granulocyte lack This reasoning was responsible for our introduction of the use of the sulfonamide drugs in the treatment of severe cases

Liver and Kidneys

In the liver most cases show areas of parenchymatous degeneration with central necrosis of the lobules and marked vacuolization of the hepatic cells The sinusoids usually are engorged with blood and the Kupffer cells are unusually prominent The kidneys usually are the site of parenchymatous degeneration

Local Necrotic Lesions

Although by clinical examination only the necrotic lesions of the mouth throat larynx skin and occasionally of the vaginal and rectal mucosae are demonstrable the process must be far more widespread particularly in the intestinal tract where bacteria normally are present in large numbers Plum analyzed the necrotic lesions of 30 fatal cases in great detail In 28 the throat chiefly in the region of the tonsils was the site of more or less extensive necroses In 8 necrotic lesions of the gastrointestinal tract were present the esophagus stomach jejunum ileum colon and rectum all being involved in more or less degree The skin showed necrotic ulcerative lesions in about a third of the fatal case

All the necrotic areas are characterized by absence of pus i e granulocytes and the presence of large numbers of bacteria The necrosis not infrequently extends deeply into the subcutaneous tissue with occasional involvement of the musculris

Clinical Features

As noted above these are entirely dependent upon the physiopathological phenomena which have been described already

Symptoms

In the individual with impending clinical agranulocytosis in whom the leukocyte and granulocyte counts are low there may be no symptoms whatever or there may be such symptoms as headache irregular elevations of temperature or weakness Severe debilitating fatigue or continued malaise may be outstanding and has been observed frequently in the cases reproduced experimentally A sharp headache may be an initial symptom An occasional individual develops an initial short febrile reaction Other premonitory symptoms which have been observed are the appearance of angioneurotic edema nausea vomiting epigastric distress insomnia restlessness etc

The first definite symptom referable to clinical agranulocytosis usually is sore throat angina The patient who by now acutely is ill with high fever and often has had a chill complains of very marked difficulty in swallowing and frequently

prominent There are plasma cells, often in large clumps lymphocytes and reticulum cells In some cases the very large number of these cells suggests a lymphoblastic or leukemic proliferation

If the patient survives the shock of the initial complete lack of granulocytes and its accompanying sepsis, the granulocyte precursors of the marrow then may reappear arising in all probability from the reticulum cells or histiocytes Myeloblasts in islands promyelocytes and/or myelocytes may be seen now Although this regenerative activity is rapidly proceeding the patient nevertheless may die of overwhelming sepsis

The appearance of the marrow at this stage is what Fitz Hugh and Krumbhaar [3] have interpreted as maturation arrest basing their view on the fact that although granulocyte precursors are present, mature granulocytes are conspicuous by their absence

This interpretation, although widely accepted and perhaps correct, does not fit in with the experimental findings of Plum The large number of myeloblasts promyelocytes and myelocytes in the absence of mature granulocytes may indicate that maturation is by no means arrested but although proceeding rapidly, has not yet reached the mature granulocyte stage Were the patient to survive another two or three days mature granulocytes might be found which might then appear in the blood stream

Without the use of antibacterial drugs such as the sulfonamides and penicillin the patient may die while on the brink of recovery At this time, the marrow may be almost normal with mature granulocytes present in fairly normal or even greater than normal numbers the blood and tissues having as yet failed to receive their normal granulocyte supply

Spleen

The spleen is soft and somewhat larger than normal corresponding to the infectious spleen seen in deaths from overwhelming sepsis Microscopically the Malpighian follicles are smaller than normal with diminished germinal centers The sinuses and pulp are engorged with red cells Reticulum cell hyperplasia and an increase in plasma cells may be noted No evidence of myeloid metaplasia has been described

Lymph Nodes

These show findings similar to those in the spleen Generally there is slight soft swelling particularly in the cervical nodes with areas of congestion and hemorrhage The germinal follicles are reduced or absent, plasma cells often are striking and bacteria in large numbers may be present

enlargement of other lymph nodes as the axillary epitrochlear or inguinal The skin particularly of the fingers and toes may show especially in the very severe cases small necrotic ulcerative lesions which like those in the mouth and throat, have no associated purulent appearance The vaginal and rectal mucosae may be the site also of necrotic ulcerative lesions Petechiae are not seen

Blood

The outstanding feature of the hematological examination is the extreme leukopenia and granulocytopenia in the presence of relatively normal hemoglobin and red cell concentrations and of normal platelet counts The leukocyte count in the typical case varies between 100 to 2 000 per cu mm Counts above 2 000 are somewhat unusual With counts above 3 000 per cu mm the diagnosis of agranulocytosis must be questioned Differential counts of the white cells in typical cases show no granulocytes whatever all the white cells being lymphocytes of the small mature variety This typical picture is subject to variation according to the time that one sees the patient and the severity of the disease In the very earliest stages of the disease the granulocytes may not be completely absent and there may be from 1 to 10 per cent of polymorphonuclear neutrophiles most of which are of the band and young forms metamyelocyte type with occasional myelocytes At this stage an eosinophile or two may be present also In the outspoken case there is complete lack of granulocytes and the lymphocytes all of the mature variety comprise the entire leukocytic population It should be noted that the absolute lymphocyte count also is distinctly lowered since with a white count of 1 000 and 100 per cent lymphocytes the absolute lymphocyte count is only 1 000 whereas the normal absolute lymphocyte count is approximately 20 per cent of 7 000 to 10 000 namely 1,400 to 2 000 per cu mm In the milder cases of agranulocytosis and in those in which spontaneous recovery is occurring there may be a definite relative increase in monocytes which may be present in proportions of from 5 to 40 per cent With an increased monocyte percentage young forms of monocytes atypical forms and histiocytes may be seen The latter are very large irregular cells with pale blue cytoplasm containing large reddish granules These generally are grouped around the nucleus which has a peculiar spongy chromatic character Rosenthal[75] and others [6] have pointed to the importance of monocytosis as an indication of good prognosis The red cells may show slight hypochromia and slight change in size and shape but are essentially within normal limits The platelets usually are abundant although in some cases they may be slightly diminished Cases in which the platelet count is very definitely depressed and the polymorphonuclears not completely lacking should make one suspect a total bone marrow lesion

of painful lymph nodes in the neck Soreness of the gums and of the buccal mucous membranes may be present

Rapidly the symptoms grow worse, being characterized by extreme malaise, high fever chills and prostration The soreness of the throat becomes more and more pronounced, and the neck may become greatly swollen On the third or fourth day of illness the patient is desperately ill and may be somewhat confused and irrational In some cases the throat lesions with their grayish white membranes suggest the picture of diphtheria In others there may be marked tonsillar swelling, resembling closely that seen in septic sore throat

Physical Examination

Physical examination reveals unusually marked prostration The patient may be disoriented Slight icterus of the sclerae is a common finding, but there is no pallor There is often a marked discrepancy between the patient s complaint of severe sore throat and the actual condition of the tonsillar fossae, which may show little more than small necrotic lesions in one of the tonsillar fossae or at the apex of the tonsils This contrast between the patient s complaints and the physical findings often is so striking that the diagnosis of agranulocytosis may be ventured The buccal mucous membranes often are partially covered with a somewhat thick ropey exudate, and the gingivae paralleling the teeth usually show whitish gray linear exudates or thin membranes Small punched out necrotic areas may be present in the gums and over various parts of the buccal mucous membranes These ulcerative areas characteristically show but little associated swelling and due to the lack of granulocytes pus is conspicuous by its absence

The lymph nodes of the neck ordinarily are slightly enlarged and tender In some cases a group of nodes on one side of the neck is greatly enlarged and apparently matted together In more severe cases the entire process may be stony hard to touch and have the characteristic appearance of Ludwig s angina Such a disturbance bilaterally is of very serious prognostic import With progression of the disease the tonsillar fossae become increasingly edematous and with it the epiglottis not infrequently becomes swollen and the site of ulcerative lesions At this point the patient may develop stridor and the symptoms of edema of the glottis Not infrequently the larynx may show similar swelling and the presence of ulcerative lesions of the true and false vocal cords

Examination of the heart and lungs ordinarily is negative, although in some cases tracheal or bronchial rales are heard Occasionally the signs of pulmonary consolidation are present The abdomen in severe cases commonly is somewhat distended The liver frequently is enlarged and somewhat tender The spleen ordinarily is not felt, and except for the cervical lymph nodes there is usually no

Plum s figures being based on a very large series of cases (114 in all) with serial sternal marrow punctures in many instances must be taken as unusually authoritative

Other Laboratory Data

Urine —The urine usually shows albumin which was present in 73 per cent of Plum s 55 fatal cases The sediment contains fine and coarse granular casts in about one half of the instances but no increase in red blood cells The concentration of urobilinogen usually is increased and bilirubin may be present

Bilirubin — Bilirubinemia of slight to moderate degree usually is found and the icterus index therefore, is increased Mixtures of direct and indirect bilirubin are found customarily indicating with the increased urinary urobilinogen that the jaundice is of hepatic origin No evidence of a hemolytic component is present

Blood Cultures —Stewart Tocantins and Jones reviewed 139 cases gathered from the literature A positive culture was obtained in 38 cases In order of frequency the organisms were streptococcus staphylococcus pneumococcus *B pyocyaneus B coli* In Plum s series of 26 cases, in which blood cultures were taken 15 howed a bacterial growth A positive culture was demonstrated in about 70 per cent of the fatal cases whereas negative cultures were obtained always in the recovered cases Thus the finding of a positive culture is of serious prognostic import a negative culture may or may not be of significance

Throat Cultures —Stewart Tocantins and Jones[1] found negative throat cultures in 16 of 68 cases investigated In the 5 cases with positive cultures streptococci staphylococci and fusiform bacilli were found most commonly with pneumococci diphtheroids etc being present in the others

Diagnosis and Differential Diagnosis

Diagnosis

In an adult acutely ill with very high fever prostration and sore throat the possibility of agranulocytosis should be considered particularly if the constitutional symptoms seem out of all proportion to the throat lesions Small necrotic ulcerations of the gums the under surface of the tongue and the buccal mucosae should be searched for In most of the cases a grayish white easily removable membranous exudate is present along the gingival margins

Although the patient is prostrated there is usually very little pallor and petechiae are hardly ever demonstrated Lymphadenopathy ordinarily is re

Sternal Bone marrow Biopsy

Biopsy of the sternal bone marrow was performed first by the trephine method which entailed a surgical operation and the removal of a button of bone [6] Because of the extreme severity of the illness in agranulocytosis, performance of even this relatively minor operation seemed in many cases a most formidable procedure Thus but few surgical biopsies are recorded, Dameshek,[74] Fitz Hugh and Krumbhaar [73] Custer The development and widespread use of the sternal puncture method has been productive of a great deal of information otherwise unobtainable Rohr [1] and Plum[10] have studied the marrow by this method in a large number of cases Both Rosenthal[78] and Plum[1] point out that the great variability in bone marrow picture as noted by various observers probably is explained by the difference in time of disease at which the marrow is removed for examination Plum by means of his experimental technique was in an unusually favorable position to study the changing picture Within a few days after the administration of aminopyrine and prior to the development of the blood picture of agranulocytosis the marrow usually showed a great reduction in granulocyte precursors myeloblasts, promyelocytes myelocytes and metamyelocytes, with only mature granulocytes remaining This was followed shortly and inevitably by the disappearance of mature granulocytes and thus by the finding of a marrow which was aplastic with respect to the granulocytes

Granulocytic aplasia is the usual finding in most of the fatal and very severe cases of the disease A common associated finding is the presence of large numbers of plasma cells which often are unusually large, and of other types of "toxic" lymphocytes It is possible that these cells which are ordinarily present in the marrow in very small numbers develop unusual regenerative activity when the marrow granulocytes disappear In some cases monocytes and histiocytes rather than plasma cells are prominent This finding which Rosenthal[78] called the reticulo endothelial type of picture is probably due either to regenerative activity of normally present reticulum cells or to their apparent increase in the marrow otherwise quite depleted of leukocytic cells

Normal marrow findings and even unusually marked leukopoiesis have been stressed by Fitz Hugh and Krumbhaar[73] and by Custer [7] This picture which they have called maturation arrest, is stated to represent the typical findings in the disease Custer for example found this type of marrow in 9 of 11 cases Typical findings, as quoted by Custer, are myeloblasts 45 1 per cent, promyelocytes 9 5 per cent, myelocytes 4 2 per cent metamyelocytes 0 6 per cent and mature granulocytes 0 0 per cent It is more than likely however, as Plum and Rosenthal point out that this finding may indicate either relative mildness of the disease or beginning recovery prior to any evidence of this in the blood picture

left with most of the cells being band and young forms Toxic granulation is a striking phenomenon the granules being off color bluish coarse large and irregularly spaced Vacuolated polymorphonuclears are seen not infrequently From the clinical standpoint the leukopenia of sep is rarely if ever is associated with the dry necrotic lesions so characteristic of agranulocytosis

Leukemia of the Aleukemic Variety — There is no doubt that many of the case diagnosed is agranulocytosis are examples of the aleukemic type of leukemia in which marked leukopenia and granulocytopenia are secondary to extensive involvement of the bone marrow Because of the marked granulopenia and its secondary effects much of the clinical picture may be indistinguishable from that of agranulocytosis There are usually high fever sore throat ulcerative and necrotic lesions of the throat buccal mucous membranes tongue and gums However, additional signs suggesting leukemia are present marked pallor generalized lymphadenopathy in the acute lymphatic type splenomegaly especially marked in the acute myelogenous type and such hemorrhagic manifestations as petechiae and ecchymoses In the buccal mucosae and in the gingivae the necrotic lesions are intermingled with petechiae and evidences of spontaneous bleeding

The blood picture is, however the determining feature in the differential diagnosis In agranulocytosis there is very little if any anemia and the platelets are present in normal numbers In leukemia anemia is striking and rapidly progressive and the platelets are conspicuous by their rarity Careful examination of the blood smear reveals that the great bulk of the white cells is composed of primitive cells either myeloblasts or lymphoblasts with very scanty cytoplasm and very large bulging nuclei compo ed of a fine chromatin meshwork in which nucleoli are prominent The morphology of these cells which are mistaken so often for ordinary lymphocytes is best studied in well prepared cover slip preparations Thick preparations and poorly made slide smears in which the white cells are present as shrunken masses are worthless for examination of the finer histological details Yet it is from such preparations that differential counts are often made and the shrunken masses above referred to called lymphocytes

The final diagosis as between aleukemic leukemia and agranulocytosis is made readily by sternal puncture In leukemia despite the lack of leukocytes in the blood the marrow is crowded with great numbers of primitive white cells with mitotic figures a prominent feature The nucleated red cells and megakaryocytes are conspicuously reduced In agranulocytosis it is the granulocytes which are reduced the nucleated red cells and megakaryocytes being hardly affected The extreme leukocytic proliferation of leukemia even of the so called aleukemic variety, gives a very striking and unmistakable picture

Pancytopenia — As noted in the discussion of leukopenia the designation of

stricted to the cervical nodes, and there is no splenomegaly These points are important if one is considering leukemia or some lymphomatous disease

The diagnosis is of course made readily by the leukocyte count and blood smear Counts above 4 000 immediately exclude the diagnosis in all except the very rare instance in which there is complete agranulocytosis in the presence of a normal or slightly low white count In fact the diagnosis of agranulocytosis must be questioned with a leukocyte count above 2,000, since the great majority of cases present counts of 2,000 or less when first discovered

The blood smear shows essentially normal appearing red cells and abundant platelets Cases with very few or no platelets should be suspected of having a generalized bone marrow disease like leukemia The leukocytes are for the most part, small lymphocytes with monocytes in varying percentages in some cases but without granulocytes Cases in which the granulocytes are stated to be 10 to 20 per cent of the total white count must be questioned many of these represent sepsis with secondary granulocytopenia but without complete lack of granulocytes The most common error is to confuse for mature lymphocytes such primitive cells as myeloblasts or lymphoblasts These differential points are discussed in the following section

The red cell count and hemoglobin concentration are within fairly normal limits Cases with well defined anemia usually have generalized involvement of the bone marrow rather than the specific leukocyte entity of agranulocytosis Nucleated red cells if found, also point to a generalized bone marrow process

The finding of leukopenia should not be the immediate occasion for the diagnosis of agranulocytosis Leukopenia is by no means agranulocytosis, leukopenia is a symptom of something wrong in the formation maturation or delivery of leukocytes from the blood forming organs usually the marrow, to the blood stream Every case showing leukopenia should, therefore be analyzed critically from this point of view before the final diagnosis of agranulocytosis is made This evaluation should not take more than a few hours of careful study

Differential Diagnosis

Sepsis with Leukopenia — Severe tonsillitis severe septic (streptococcic) sore throat, septicemia with multiple lesions including those of the throat and numerous other infectious diseases may show well marked leukopenia Oftentimes the diagnosis of agranulocytosis is made simply from this finding The leukopenia of sepsis rarely is less than 3 000 per cu mm and the differential count is strikingly different in that there are usually at least 50 per cent of granulocytes Only rarely are the granulocytes reduced below 20 to 30 per cent Careful differential counts disclose the presence under these conditions of a marked shift to the

only slight swelling of the tonsillar tissue or of remaining tabs of lymphoid tissue is seen The patient ordinarily is only slightly ill and gives the appearance of well being on first inspection quite in contrast to the clinical picture of agranulocytosis in which severe prostration and high fever are usual There is furthermore, generalized lymphadenopathy and frequently splenomegaly although one hastens to add that both of these features are lacking occasionally

Inspection of the blood smear in infectious mononucleosis reveals a well marked lymphocytosis which is characterized by extreme variability in size shape and staining characteristics of the lymphocytes contrasting with the sameness of the lymphocyte morphology of agranulocytosis Furthermore there are in most cases from 10 to 20 per cent of cells other than lymphocytes usually mature granulocytes band form polymorphonuclears and a few monocytes

However, in those cases in which there still is some doubt the heterophile agglutination test of Paul and Bunnel using sheep s red cell usually clinches the diagnosis In infectious mononucleosis particularly in the severe cases the test is positive in serum dilutions of 1 to 16 or higher In agranulocytosis the test uniformly is negative Although one should be able to make the diagnosis of infectious mononucleosis by the clinical picture and hematological findings it is nevertheless comforting to obtain a positive heterophile reaction in a case in which such very serious conditions as leukemia or agranulocytosis have been considered

Prognosis

Once the diagnosis of agranulocytosis has been established in a given case the prognosis must be considered exceedingly grave Plum states that most of the fairly large collections of cases show a mortality amounting to 70–90 per cent In his own series of 88 cases the largest individually studied 74 died a mortality rate of 84 per cent Of 30 cases observed by me between 1936 and 1941 only 2 recovered both being relatively mild in nature On the other hand Kracke[4] states that approximately 50 per cent of the cases recover whereas in earlier years the mortality rate was from 80 to 90 per cent This has not been my experience however Of 12 cases which I reported in 1936 8 recovered whereas in the succeeding 5 years 28 of 30 died Jackson and Tighe (1939) analyzed 390 cases and concluded that the outlook depended largely upon the type of treatment given with the lowest mortality rates 35 per cent or less being found in cases treated with pentose nucleotides adenine sulfate leukocytic cream and yellow bone marrow extract

Numerous factors such as age previous state of health etc undoubtedly enter into the prognosis of a given case but my own impression is that the most important ones are the dosage of the offending drug the degree of leukopenic

pancytopenia may be applied to conditions in the blood in which there is a well defined reduction in red cells, white cells and platelets The finding of leukopenia in association with anemia and thrombopenia ordinarily is indicative of some type of bone marrow disturbance Whether this is due (a) to a bone marrow lesion such as hypoplasia, aplasia, leukemic infiltration, metastatic involvement, replacement of marrow by other abnormal tissue, fibrosis etc , (b) to splenic inhibitory effects or (c) to maturation arrest as in pernicious anemia must be worked out for each individual case In any event, when anemia and thrombopenia are found simultaneously with leukopenia, the diagnosis of true, ' primary agranulocytosis must be questioned seriously and some bone marrow, splenic or deficiency syndrome be considered

There can be no question that the clinical picture of agranulocytosis with all its various features, high fever, prostration, necrotic lesions of the mouth and throat, can be found in the severe granulocytopenia of bone marrow and occasionally, of splenic disease This is due simply to the fact that with complete or almost complete absence of granulocytes from the blood and tissues for what ever cause there will inevitably be marked flourishing of the bacteria normally present in the oral and pharyngeal cavities

Thus in the pancytopenia of leukemia acute or chronic in occasional cases of Hodgkin s disease in certain cases of aplastic anemia and in occasional instances of splenic disease with severe neutropenia the typical clinical features of agranulocytosis are seen These cases may be designated as examples of secondary agranulocytosis, the term primary being reserved for those in which a drug, notably aminopyrine causes a selective disturbance of the leukopoietic tissue of the marrow without involvement of the erythroblastic or megakaryocytic tissue

Such cases of secondary agranulocytosis should be differentiated quickly from the primary type once it is recognized that anemia is an important concomitant of the leukopenia This done search must be made for petechiae indicating platelet deficiency lymphadenopathy indicating lymphatic leukemia lymphosarcoma, Hodgkin s disease, splenomegaly jaundice etc The blood smear should give important information with respect to platelets and primitive leukocytes Sternal puncture often is diagnostic of the fundamental condition

Infectious Mononucleosis — This infectious disease involving lymphoid tissue ordinarily is associated with leukocytosis of moderate degree 15,000 to 30,000, but in about 10 per cent of all cases leukopenia is present In rare instances the leukocyte count is reduced to 2 000 per cu mm or less In such situations with the differential count showing 80–90 per cent of lymphocytic cells and but few granulocytes the diagnosis of agranulocytosis may well be entertained since one of the clinical features of both diseases is the sore throat However, except in rare instances the angina of infectious mononucleosis is relatively mild, and

Certain Guiding Principles in Prognosis

Dosage of Drug — If this can be determined which usually is a difficult procedure in a patient so seriously ill one important prognostic point is immediately apparent since the larger the dosage the worse the prognosis

Age — The older the patient the worse the prognosis This is of course applicable to all infections and most illnesses A patient over 60 years of age has hardly any chance It should be noted however that one of our patients aged 80 years made an excellent recovery when given sulfathiazole [a]

Constitutional Symptoms — The greater the patient s prostration appearance of anxiety confusion inactivity and drowsiness the worse are his chances In fact Plum found that only those individuals who were perfectly rational on admission stood some chance of recovery A quick inspection often is of more importance in prognosis than almost any other test

Extent of Necrotic Lesions — If the skin is involved with necrotic areas a fatal result may be expected (Plum) It should be noted however that extensive skin necroses were present in one of our cases treated with sulfathiazole and recovery occurred

Leukocyte and Differential Counts — The lower the total leukocyte count the worse the outlook Patients with counts under 1 000 almost all die those with counts above 2 000 frequently recover A complete lack of granulocytes may be present in either instance and is therefore of no great prognostic import However the presence of definite monocytosis is indicative of beginning convalescence and therefore of a good prognosis The sternal puncture may be helpful also in this regard if the marrow shows normal or fairly normal numbers of granulocytes the outlook is reasonably good providing infection can be staved off In a marrow which shows only lymphocytes the outlook is extremely bad and perhaps hopeless

TREATMENT

The treatment of agranulocytosis is today far from satisfactory No specific method has as yet been found which will definitely result in the proliferation of the granulocytic cells of the marrow Many such methods have been introduced and have had their adherents but the evidence of their effectiveness is far from clear In the treatment of a given patient who usually is desperately ill it is the custom dictated by necessity to use 3 or 4 methods together hoping thereby that if one is of no real value perhaps one of the other measures which have been recommended might be successful

A long list of therapeutic agents has been introduced at one time or another

shock which the patient develops and his ability to recover from it and finally the patient s ability to withstand the sepsis secondary to the lack of granulocytes

In an individual, who has become sensitized to aminopyrine, the administration of 0 3 to 0 6 gm (gr 5 to 10) of the drug orally will result as shown above in marked leukopenia, granulocytopenia and perhaps, complete agranulocytosis with a varying, usually mild constitutional reaction, from which the patient generally makes a quick recovery The situation is quite different however in a similar individual who has taken aminopyrine in doses of 0 6 gm (gr 10) several times daily for 2 to 3 days Under such circumstances the entire leukopoietic tissue must inevitably be so completely shocked that recovery might become impossible In other words a small dose of drug may affect a relatively small amount of marrow tissue and allow a natural recovery with a large dose the injury may be so widespread that recovery is impossible That these possibilities are likely is brought out in the histories of recovered cases who later have been tested for sensitivity Their initial severe illness with outstanding constitutional symptoms came on following the use of several doses of aminopyrine a single small dose later on produced only a mild state

It should be realized also that there is always an interplay between the size of the dose and the degree of hypersensitivity of the individual The more hypersensitive the individual the smaller will be the dose required to produce the disease and vice versa

In general therefore the outlook is poorest in the most sensitive individual and particularly in those who just prior to the disease have taken several doses of the drug over a period of 2 or 3 days or longer To a large extent the amount of granulopoietic recovery probably is dependent upon the severity of the secondary infectious state the degree of bacterial invasion of the blood and tissues and the patient s immunity to the invading organisms It is under these circumstances that the bacteriostatic drugs such as the sulfonamides and penicillin probably will be exceedingly useful Whether any other therapeutic method offers anything under such circumstances is a matter of opinion It is my own impression that the therapeutic efficacy of transfusion liver extract yellow bone marrow extract, pentose nucleotides adenine sulfate etc has been greatly overrated and that treatment except with the sulfonamides probably does not alter the course of the disease

Recovery if it occurs is dependent upon the individual being able (a) to cope with the shock of the granulocytopenia by his own cellular reactivity and (b) to combat the bacterial invasion which occurs inevitably in a body stripped of its granulocyte defenses Of these two the ability to conquer the bacterial invasion perhaps is the most important since granulocytopenia per se is compatible with life

granulopoiesis I have observed this in relationship to erythropoiesis and repeated transfusions

Transfusions from individuals with high leukocyte counts have been proposed I have used blood from polycythemic patients who generally have a white count about twice the normal and from donors who have been given an intramuscular injection of 10 c c of milk about an hour prior to venesection By this means the leukocyte count often can be increased to twice its original level Others have reported good results with the use of blood from patients with chronic myelogenous leukemia This appears to be a logical procedure since if a transfusion of 500 c c of blood from an individual with a 200 000 leukocyte count is given the immediate theoretical increase in white cells is about 20 000 per cu mm To be sure not all of the granulocytes are physiologically active since it is only the metamyelocytes and mature polymorphonuclears which are motile in supravital preparations However one may expect a very definite increase in leukocytes which at the site of the necrotic ulcerations will presumably be active in combatting bacterial spread The possible dangers involved in the transfusion of leukemic blood need not seriously be considered Firstly the patient is so critically ill that the first consideration is to save his life Secondly it has been found impossible to transmit leukemia in humans by the transfusion of chronic leukemic blood[3] although it is theoretically possible but as yet not demonstrated to transmit acute leukemia in which large numbers of primitive cells are present

From the practical standpoint it is very difficult to have at hand (a) an untreated case of chronic myelogenous leukemia (b) with very high leukocyte counts and (c) of the same blood group as the patient with agranulocytosis and (d) whose physician or for that matter the patient himself is willing to permit the withdrawal of 500 c c of blood For one reason or another the correct set of circumstances rarely is present

The mortality rate for cases given transfusions alone as the chief therapeutic agent is 67 per cent This corresponds fairly closely to the general mortality rate

To summarize therefore transfusions of normal blood in a case of agranulocytosis probably are without effect on the disease although they may have some psychological value for the patient s family Multiple transfusions may conceivably depress bone marrow function and thus prevent the normal recovery from the initial leukopenic shock If given at all the blood of donors with elevated leukocyte counts should be used donors with chronic myelogenous leukemia if obtainable and compatible are preferred

Nucleic Acid Derivatives — One of the chief constituents of the leukocyte is nucleic acid Nuclein therapy to increase the germicidal power of the blood was

during the past two decades In part they are as follows x ray therapy over the bones, transfusions of blood nucleic acid derivatives including pentose nucleotides and adenine sulfate leukocytic cream liver extract, yellow bone marrow as such or in extract form, foreign proteins and more recently, the sulfonamide drugs Because of the relatively few cases of the disease under the care of any one individual or group and because each case is critically ill on admission to the hospital it has been difficult, if not impossible, to make control observations or even to evaluate properly the relative merits of the various methods of therapy

Therapeutic Agents

X ray Treatment — This was introduced by Friedemann[41] in 1928 the rationale being that while ordinary doses of x ray might depress leukopoietic tissue small doses might irritate it and thus stimulate the production of new leukocytes In 1930 Friedemann and Elkeles[8] reported their results in the treatment of 43 cases X ray was given as 1/20 of a skin erythema dose with a 0 6 mm copper filter over the long bones the scapulae the sternum and the pelvis There were 30 deaths, 70 per cent mortality and the recoveries all occurred in a selected group of 15 patients, who had neither sepsis pneumonia nor a quick death after the institution of therapy Lichtenstein[63] (1932) reported 17 cases treated in the same way with 5 recoveries Of these 3 had shown immature granulocytes impending recovery(?), prior to treatment Jackson and Tighe in their survey of 390 cases variously treated found that the mortality rate in those treated with x ray was 67 per cent It may be stated quite definitely, therefore, that x ray therapy is of no value

Transfusions — These have been given by almost all observers since agranulocytosis was first described as a disease entity The rationale involved is the addition of granulocytes to a circulation which is practically devoid of them If a transfusion of 500 c c of blood containing 10 000 white cells per cu mm is given to an individual with a normal 5 000 c c blood volume it is theoretically possible that an increase of 1 000 leukocytes per cu mm will develop Actually, due to the various circumstances involved in collecting and giving blood the total leukocyte count usually rises no more than 500 per cu mm Of these no more than 70 per cent are granulocytes The transfused granulocytes probably last no more than a few hours at most in the circulation One wonders how many of them actually arrive physiologically intact at the sites of bacterial invasion

A number of transfusions say 4 given at intervals of several hours might conceivably raise the total leukocyte count 2 000 to 4 000 per cu mm Actually I have never seen this happen Furthermore, it is probable that repeated transfusions inhibit normal bone marrow growth and actually prevent recovery of

Pentose Nucleotides — Because the pentose nucleotides pentnucleotides have been so widely advertised and used in the treatment of agranulocytosis and because many physicians believe they are of specific value in the treatment of the disease it is important to analyze critically the initial therapeutic results of Jackson and his co workers as published in 1931 Of the 7 cases listed as typical agranulocytic angina and which recovered after treatment with pentose nucleotides the first one Case 7 had a rather slow illness with fever the first recorded leukocyte count was 3 700 with 70 per cent granulocytes Six days later the white count fell to 1 200 with no granulocytes and the patient made a gradual recovery following treatment with daily doses of 0 7 gm of pentose nucleotide intravenously In this relatively mild slowly developing case the factor of spontaneous recovery cannot be ruled out with certainty Case 8 a boy aged 10 had very marked hepato and splenomegaly and a leukocyte count of 1 500 per cu mm there is no report on the differential counts This case can hardly be classed as a typical example of agranulocytosis Case 13 with a smoldering pulmonary tuberculosis for 20 years and a readily palpable spleen seemed otherwise to have been a typical example of the disease which recovered after treatment with pentnucleotide therapy Case 14 also seemed quite typical of the disease In Case 16 the initial leukocyte count was 2 500 and the differential count showed 56 per cent lymphocytes and 44 per cent monocytes 0 6 gm of nucleotide was given intravenously on the day of admission On the following day the polymorphonuclear count was 27 per cent This case with premonitory monocytosis and with a well marked granulocyte count the day after institution of treatment must be classed as one of spontaneous recovery In Case 18 there was evidently a chronic leukopenia and neutropenia and the leukocyte count when treatment was begun was 3 500 per cu mm In this case chronic rectal pain and an extremely tender mass in the rectum were outstanding features no mention of sore throat was made Here too one cannot consider this as a typical example of agranulocytic angina the possibility of a chronic infection in the rectum or ischiorectal fossa was not ruled out and the granulocytes continued low upon the patient s recovery from his agranulocytic state In Case 19 several relapses occurred in 2 of which nucleotide was given In this subacute or chronic case which cannot be considered as a typical example of the disease the factor of spontaneous recovery cannot be ruled out It is also unfortunate that a control period without treatment could not have been carried out in one of the relapses

Thus of 7 cases classed as typical and which were said to show a regular pattern of recovery only 4 may be considered as truly characteristic cases of the disease One case was almost certainly not agranulocytosis one case probably was an example of chronic infection in the rectum or ischiorectal fossa in

suggested as early as 1893 by Vaughan, Novy, and McClintock[86] In 1897 Ames and Huntley[87] suggested the use of nucleinates 1 5 to 2 8 c c were injected intramuscularly in dogs to induce leukocytosis Habetin[89] later (1923) used 10 c c of a 50 per cent solution of sodium nucleinate in a wide variety of human cases

Doan Zerfas, Warren and Ames[90] (1928) set out to study the effect of various substances on the delivery of leukocytes from the bone marrow to various tissues They found that sodium nucleinate in relatively large doses was productive of a marked leukocytosis in rabbits although an initial leukopenia usually occurred In an attempt to avoid the leukopenia and produce only leukocytosis study was made of the degradation products of nucleic acid This large molecule is made up of 4 nucleotides each of which in turn is composed of a purine or pyrimidine base linked with the saccharide pentose and with phosphoric acid These bases may be detached from their linkage, treated with acids such as hydrochloric and sulfuric to form adenylic and guanylic acids or hydrochlorides or sulfates Doan and his co workers found that chemically pure crystalline adenylic and guanylic acids evoked an immediate neutrophilic response without preliminary leukopenia suggesting that they were preferable to the larger nucleinate molecule for clinical use Reznikoff [4] and Jackson Parker, Rinehart and Taylor were the first to use these substances in the treatment of agranulocytosis

Reznikoff treated 4 cases with among other measures, adenine sulfate or guanidine hydrochloride 3 of these cases recovered Later he reported[91] on the treatment of 15 cases with 11 recoveries Jackson who had worked with the nucleotides for a number of years having been the first to isolate them from the blood (1924) used the ' unbroken pentose nucleotides in a series of 20 cases of profound leukopenia, 13 of which were stated to be examples of typical agranulocytosis Seven of the later cases recovered Jackson and his co workers stated that in all cases the first definite sign of clinical improvement occurred on the third or fourth day after treatment was instituted hematological improvement occurring later They emphasized this consistency likening it to the clinical feeling of well being and the reticulocytosis which occur in pernicious anemia following treatment with liver extract Five cases apparently differing in no way from those which recovered showed neither clinical nor hematological improvement One case died after an initial improvement In a later report[92] (1932) the treatment of 69 cases was reviewed this series consisted of the 20 cases above referred to, of which only 13 were stated earlier to be typical examples of agranulocytosis, together with 49 cases treated by various observers in various parts of the country and for which very little data are given Seventy four per cent of the cases recovered In a still later analysis of 85 cases by Jackson and Tighe[80] the recovery rate was found to be 65 per cent

distress bradycardia chills and sweating this method of administration has been largely abandoned in favor of the intramuscular route Injection of 40 c c of pentnucleotide 4 ampoules each containing 0 7 gm of nucleotides is recommended as a daily dose This is a rather large amount for daily injection even in those with thick muscled glutei Reactions are not infrequent chills flush a sensation of generalized itching or burning periods of temporary confusion feelings of inward excitement followed by semi stupor and dullness etc These often can be avoided by the simultaneous administration of small doses of adrenalin chloride or atropine sulfate subcutaneously

Adenine Sulfate — As noted above this is the sulfate of adenylic acid one of the purine bases which has been freed of its linkage with pentose and phosphoric acid Reznikoff [4] (1930) was the first to use this material in the treatment of 4 cases of which 3 recovered However in neither this nor a later report (1933) were the cases well controlled

Adenine sulfate (obtained usually in 10 gm lots from Eastman Kodak Co price approximately $15) is dissolved in 1 or 2 gm amounts in 50 to 100 c c of distilled water The drug is difficultly soluble heating being necessary preferably over a water bath to bring it into solution Solution may be facilitated by the addition of 1 to 2 drops of 0 1 normal hydrochloric acid The final solution is injected after being allowed to cool to body temperature either intravenously or intramuscularly The intravenous route by the drip method is preferable because of the lack of local reaction With repeated intravenous injections which usually are given daily the vein may become occluded General reactions are rare

Jackson and Tighe [9] analyzed the records of 10 typical cases receiving adequate amounts of adenine sulfate and found that of these only 2 died They stated that this relatively low mortality indicated that a more extensive trial of the drug should be given My own impression [81] has been that adenine sulfate might be the active principle of the pentose nucleotides and that its intravenous administration was productive of a quicker and more potent therapeutic response than that induced by the pentose nucleotides I have since had occasion to modify this rather optimistic viewpoint and believe now that its value is questionable However in a desperate situation it is worthy of trial and certainly is not harmful

Leukocytic Cream — The use of leukocytic cream the buffy coat of the blood as collected by centrifugation in Babcock cream bottles was suggested by Struma who was impressed with the theory that normal stimulation of granulocyte production was due to the material (nucleic acid salts?) liberated from the break down of old cells He believed that the injection of leukocytes intramuscularly might furnish such active and well tolerated material

The preparation of leukocytic cream from whole blood is a laborious and

one case spontaneous recovery almost certainly took place, and in the others the factor of spontaneous recovery cannot be ruled out The 6 cases, which died were for the most part more typical examples of the disease

In their report of 1932 Jackson, Parker and Taylor[91] analyzed 69 cases of severe leukopenia, including the 20 previously reported Details of these cases, which were treated with pentnucleotides by various observers in various parts of the country were not given The constancy with which improvement began about the fifth day of treatment irrespective of the duration of the disease, was believed an important indication of the effectiveness of the product Of 54 cases classed as typical, 38 70 per cent, recovered However it should be noted that all patients the number is not specified who died less than 72 hours after treatment was begun or those in whom treatment was discontinued within this period, were excluded from the report and the mortality statistics This method of selection has been criticized by many observers

In 1937 Jackson and Tighe analyzed 390 cases of agranulocytosis variously treated None of the cases previously reported are included in this series All cases which terminated fatally within 48 hours or which showed signs of recovery within 72 hours or which were treated with less than 20 c c of pentnucleotide intramuscularly daily were excluded from consideration Forty one cases thus selected received pentnucleotides alone in this group the mortality rate was 29 per cent Another 44 cases received pentnucleotide together with other forms of therapy here the mortality rate was 40 per cent A large number of cases, 130 was put into the group of inadequately treated in this group the mortality rate was 73 per cent

The data as to the efficacy of the pentose nucleotides in the treatment of agranulocytosis must be considered as far from satisfactory The apparently favorable results of Jackson and co workers must be tempered by their exclusion of all cases which died within 72 hours (first and second series) or 48 hours (third series) and by consideration of the important factor of spontaneous recovery It stands to reason that those cases still alive after 2 or 3 days of treatment present a far better chance for recovery spontaneous or otherwise, than those sicker ones which die within that period My own impression regarding the value of the pentnucleotide has altered greatly in the last decade At present I consider it of only doubtful value although the possibility that the drug is of value cannot be excluded When faced with a disease of such violent intensity as agranulocytosis, one is perhaps justified in using any measure which offers any possibility of help

The pentose nucleotides, originally called K 96 were first given by the intravenous route in doses of 0 7 gm daily dissolved in 10 c c of distilled water Because of the frequency of such violent reactions as extreme dyspnea, precordial

of granulocytes the further intensive use of liver extract was ineffective and the patient died

Powers and Murphy [5] noted that the parenteral injection of liver extract protein free in normal subjects induced a well defined leukocytosis This together with the effect on the leukocyte count in pernicious anemia led Murphy [6] to use parenteral liver extract in agranulocytosis with gratifying results

Jackson and Tighe [9] concluded from their statistical survey of therapy that the mortality rate for cases treated with liver extract was 62 per cent Whether the advocates of liver extract therapy would agree with the methods of these authors for handling the statistical material is a matter of question In any event it would seem that liver extract therapy has little if any rational relationship to agranulocytosis and that most of the favorable results probably are spontaneous in origin Two advantageous features of liver extract should however be mentioned (1) it does no harm (2) it is readily available Whether these features represent any greater indication for its use in agranulocytosis than intravenous salt solution for example is debatable

Yellow Bone Marrow and Its Extract — According to Marberg and Wiles [7] Watkins announced in 1933 that a strained preparation of yellow bone marrow had been beneficial in various cases associated with a low granulocyte count One of the pharmaceutical houses (Armour & Co Chicago) produced a fat free concentrate of yellow bone marrow which was given orally in 0 3 c c to 5 c c doses several times daily in treatment of 10 cases of leukopenia Only 2 of these cases 4 and 7 appeared to be typical examples of agranulocytosis in both of which other methods of treatment including pentose nucleotides were used also The other 8 cases included the leukopenia of various infectious states malignancy x ray therapy etc That the therapeutic results obtained with yellow bone marrow extract were at all related to the use of this preparation must be questioned

Giffin and Watkins[98] reported on the treatment of 24 cases which were given bone marrow extract as the sole medication Unfortunately the data regarding the cases are not presented in sufficient detail for critical analysis

That an extract of yellow bone marrow its most inactive portion should be effective in the treatment of sudden cessation of leukopoietic growth is questionable especially when it is considered that the material is given by mouth in relatively small dosage Its further use in the treatment of agranulocytosis appears debatable

Antibacterial Agents Including the Sulfonamides and Penicillin — Death in agranulocytosis probably is due not to the lack of granulocytes as such but to the bacteremia and septicemia which inevitably ensue As pointed out above spontaneous recovery of granulopoiesis occurs almost invariably if the dose of drug

highly specialized procedure, which is difficult to carry out except in laboratories equipped with large centrifuges and centrifuge heads, special bottles and technical personnel specially trained in the aseptic handling of glassware Once obtained, the cream from 100 to 150 c c of whole normal human blood is injected intramuscularly daily Of 12 cases treated 2 died, a mortality rate of 17 per cent A favorable response is expected in from 1 to 3 days In a recent personal communication Strumia[93] stated that of 25 cases of typical agranulocytosis treated with leukocytic cream 22 recovered The 3 deaths occurred in patients with severe total marrow hypoplasia

Strumia frankly stated in his original publication that ' unquestionably some of the milder cases would have recovered spontaneously , on the other hand, extremely acute fulminating cases are probably not helped by any therapeutic measure ' It is likely that the difficulty of preparing fresh leukocytic cream has acted as a strong deterrent to its further use Its actual efficacy must remain an open question, only to be determined by control observations, these are unfortunately lacking However, Strumia s excellent results make this method one to be seriously studied

Liver Extract —The remarkable therapeutic effect of liver extract in pernicious anemia naturally has led to its wide use in all the various blood dyscrasias Unfortunately it is only of value when liver extract factor is lacking This occurs in pernicious anemia and perhaps in one or two closely related deficiency syndromes The administration of liver extract has no stimulating maturing or other action on the normal or abnormal marrow, in the presence of a specific deficiency it supplies the missing factor if no such deficiency exists in cases showing severe anemia, leukopenia or thrombopenia it is probable that the material is wasted

The development of leukocytosis following liver extract therapy in pernicious anemia had been noted by many observers This fact coupled with the idea that agranulocytosis was due probably to a defective function of the marrow led Foran, Sheaff and Trimmer[94] (1933) to use liver extract in its treatment Of 5 cases treated 4 recovered The intravenous route was utilized in the more acute cases the liver extract being diluted to 20 c c with distilled water and injected slowly every eight hours over a period of five minutes In the less acute cases the intramuscular or oral routes were used It is to be noted that in 3 of the 5 cases the initial white counts were 2 200, 2 300 and 1 400 per cu mm with 14 8 and 17 per cent granulocytes respectively spontaneous remissions with similar counts have been common in Plum s series Also of interest is that in Case 4 recovery apparently occurred with liver extract when the leukocyte count was 1,400 with 17 per cent granulocytes but when the patient relapsed while taking liver extract, and had a leukocyte count of 650 per cu mm with complete absence

by another drug such as aminopyrine In a case of sulfadiazine induced agranulocytosis sulfathiazole may be used since the patient may have developed a highly specific sensitivity to sulfadiazine

The recent development of penicillin as an antibacterial agent free from all reactivity upon the bone marrow promises to be of great value in the treatment of agranulocytosis In their report on the treatment of 500 cases of various infections Keefer and collaborators list one case of agranulocytosis in which recovery occurred following the administration of penicillin It seems likely that this drug as it becomes readily available will prove to be the method of choice in the treatment of agranulocytosis particularly in those cases due to the sulfonamide drugs

Summary of Methods of Treatment

The various methods which have been utilized in the treatment of agranulocytosis have all been introduced with more or less eclat and always with favorable mortality statistics Their very number suggests that none of them is specific To assay their real value would require either a good animal method for the production of agranulocytosis or the collection of a large number of suitable control cases either untreated or treated by various single therapeutic methods Unfortunately neither of these desiderata has been realized The cases of agranulocytosis are relatively few in number and furthermore they are so desperately ill that medications offering any therapeutic hope at all are given indiscriminately As Reznikoff states[1] I have not kept any statistical data on the therapeutic value of the various measures used in the treatment of agranulocytosis because I am convinced that none of them is specific My method is to use anything that may help the patient and will not hurt him Therefore I give liver extract yellow bone marrow nucleotide in gradually increasing doses and if the referring physician insists upon it transfusions Patients recover spontaneously or die no matter what treatment is given them

A patient who has become sensitized to a drug and who later has received a large dose of it may never recover the granulopoietic production of his marrow this patient probably will die no matter what treatment is given Even here however it is desirable to control the inevitable infection A sensitized patient given a moderate amount of the antigenic drug has the possibility of granulopoietic recovery unless he dies meanwhile of sepsis Infection can be controlled by the sulfonamides or penicillin thus allowing the bone marrow time for a possible spontaneous recovery Whether granulocyte production is under these conditions aided by pentose nucleotides adenine sulfate liver extract or yellow bone marrow extract is open to question My own feeling shared by Plum is that it is difficult to imagine that the bone marrow of the infected and intoxi

such as aminopyrine has been small. The period involved in this bone marrow recovery, during which the blood and tissues are depleted of granulocytes is a critical one. It is during this time that bacterial growth flourishes unimpeded and bacteremia and finally generalized sepsis may occur. The patient thus may die of sepsis during spontaneous bone marrow recovery. Treatment of the secondary infection hence becomes of great and perhaps paramount importance.

These considerations led the author [6] to suggest the use of the sulfonamide drugs in the treatment of agranulocytosis, especially since according to many observers it has been shown that they act as bacteriostatic agents without the mediation of the leukocytes. In two desperately ill patients, one of whom was over 80 years of age, recovery ensued following the use, among other medications, of sulfathiazole. In both cases the situation was, according to the statistics of Plum, a hopeless one. In the first case, a man aged 43, the leukocyte count was 500 per cu. mm. with complete absence of granulocytes. The patient was disoriented, frequently comatose, had bilateral pneumonia and many necrotic lesions of the skin. The sternal marrow showed complete absence of granulocytes. Despite all these unfavorable features the patient made a complete recovery following the use of sulfathiazole. In the second case, a woman aged 81, apparently dying and with a leukocyte count of 500 per cu. mm., recovery also ensued. In both of these cases transfusions and pentnucleotides were given also, so that the exact value of the sulfonamide drug could hardly be assayed. However, there can be no question that the drug did no harm; its use is justified furthermore on theoretical grounds.

In several cases seen since the first report it has become clear (a) that the patient can be kept alive and free from sepsis with continued administration of the drug and (b) that under such conditions granulopoiesis spontaneously occurs. Too long an administration of the sulfonamide drug should, however, be avoided because of the possibility that the drug itself may delay granulocyte production. In a more recently observed case sulfadiazine was begun when the leukocyte count was 300 per cu. mm. and was continued in either 3.0 or 6.0 gm. dosage for 10 days. At the end of that time the patient's white count was still only 400 per cu. mm. although she was otherwise in good condition. Sulfadiazine thereupon was discontinued and the leukocyte count rose to 900, 1,700, 3,800 and 8,400 on successive days.

Recent animal experiments in guinea pigs with both sulfathiazole and sulfadiazine indicate that the latter drug frequently resulted in well defined leukopenia and granulopenia after continued administration; sulfathiazole, perhaps because of its lessened solubility, failed to diminish the leukocyte counts in the animals studied. For this reason sulfathiazole may be the drug of preference in agranulocytosis. That the sulfonamide drugs are occasionally themselves the initiators of agranulocytosis should by no means be a deterrent to their uses in a case induced

of proprietary medications he prescribes particularly if they are said to be analgesic in quality or better he should use only simple well known preparations such as aspirin codeine and phenobarbital either singly or in combination For the lay public frequently misled by extravagant radio and newspaper advertising and given to much self dosage there is unfortunately real danger Continued publicity by the medical profession and by social organizations might conceivably be of some assistance but against high pressure advertising this help is minimal The only real way of destroying the aminopyrine menace is to legislate the drug out of existence Those physicians who still hold that the drug has preeminent therapeutic value and very little if any danger could perhaps prescribe it in non refillable prescriptions

With respect to the sulfonamide drugs and the arsphenamine preparations these chemicals are at the present time specific and irreplaceable therapeutic agents Their use must therefore be continued although their potential dangers are well known With administration of sulfonamide drugs several rules are in order

(a) perform a leukocyte count every 2 or 3 days

(b) beware of too long continued administration since many cases have occurred after 7 days of continuous therapy If the drug has not proved its value in aproximately 4 or 5 days probably it will not be effective beyond that period

(c) beware of intermittent and half hearted administration

The sulfonamide drugs are given often in small dosage for such vague indications as grippe sore throat fever of unknown origin etc Their use generally is discontinued after a few days only to be restarted in a few days when the temperature has again risen Many cases of sulfonamide agranulocytosis presenting this or a similar type of history suggest the development of hypersensitivity These cases are particularly tragic because they need not have occurred The use of the sulfonamide drugs should be limited to the pyogenic infections including those due to the streptococcus staphylococcus meningococcus gonococcus and pneumococcus organisms In addition in urinary tract infections due to *B coli* the sulfonamides appear to have definite value In rheumatic fever influenza primary atypical pneumonia grippe infectious mononucleosis and a host of other infections due to non pyogenic bacteria viruses parasites and fungi the drugs have no value often indeed they appear to make the patient worse If on the other hand a secondary pyogenic infection can be demonstrated in these or in any other illness the sulfonamides may be used then Their use in the attempted prevention of gonorrhea probably is to be deplored because sensitization may develop When as in the armed services the drug must be given later for a really serious condition there is the definite possibility that agranulocytosis may occur The same warning must be sounded with respect to the pro

cated agranulocytosis patient could require more stimulation than it receives from the infection already present"

The ideal treatment, if it could be carried out, would be

(a) discontinuance of the offending drugs with particular reference to amino pyrine,

(b) symptomatic care, with the administration of sufficient fluids, salt, glu cose either orally or parenterally,

(c) administration of one of the sulfonamides, preferably sulfathiazole in full dosage for not more than 5 days, or of penicillin if available,

(d) administration of viable leukocytes by transfusion from a suitable case, if available, of chronic myelogenous leukemia

Transfusions of whole normal blood, the use of pentose nucleotides, adenine sulfate yellow bone marrow extract and liver extract are in my experience, of no or doubtful value This may be too sweeping a generalization and as Sturgis[1 1] states I do not think that up to the present time there has been definitive proof produced which would lead one to abandon all of these forms of therapy I still think, in the absence of specific measures that some of them are worth a trial ' Until the accumulation of more data unobscured by polytherapy the matter must at present rest there

Prophylaxis

Probably the most important consideration in agranulocytosis is not its therapy which admittedly is unsatisfactory, but its prevention Of primary impor *tance here is the complete discontinuance of any drug (a) which may* be harm ful to granulopoiesis and (b) which can be replaced by a harmless drug of compa rable or perhaps somewhat less comparable therapeutic value Aminopyrine fulfills both these criteria it has been shown to be harmful to granulopoiesis, and it can be replaced without too much hardship by aspirin codeine, etc On the other hand the arsphenamine derivatives and the sulfonamide drugs, although potentially harmful, are for certain specific purposes wholly irreplaceable

The case against aminopyrine has already been presented above In the little country of Denmark prophylaxis has been practised on a large scale by simply legislating the drug out of use[10] Coincidentally, as Plum has shown the num ber of cases of agranulocytosis has fallen precipitously In this country there is still a large number of proprietary preparations which contain, usually in combi nation with some other drug aminopyrine or a closely related chemical Unfor tunately no sweeping legislation banning these drugs either singly or in combina tion has been made either by Congress or by any of the state legislatures Under these conditions it behooves the practising physician to note carefully the types

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phylactic use of the sulfonamides in cases of rheumatic fever It appears that although these drugs are without value in rheumatic fever itself they are probably effective in controlling relapses of the disease, which may be associated with invasion by the hemolytic streptococcus[10]

In summary, if it is realized that drugs are chemicals, and that some of them have outspoken effects on the bone marrow either directly or through various sensitization phenomena, their use will be attended with appropriate caution

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CHAPTER XXIII

SICKLE CELL ANEMIA

By M. M. WINTROBE

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Definition.—Sickle cell anemia is an hereditary familial disease essentially peculiar to negroes which is characterized clinically by symptoms of anemia, rheumatoid manifestations, acute attacks of pain and leg ulcers and is marked hematologically by the presence of peculiar sickle- and oat shaped red corpuscles and an hemolytic anemia. The tendency to form such abnormally shaped red corpuscles unaccompanied by hemolytic anemia is known as the sickle cell trait.

HISTORY

J. B. Herrick first observed this disorder in a colored medical student in Chicago in 1910. It is now clear that the syndrome described by

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Herrick differs from the congenital abnormality, reported by Dresbach in 1904, in which a large proportion of the red corpuscles are found to be elliptical. Such cells do not alter their form when deprived of oxygen as do the erythrocytes of the sickle cell disorder. A few years after Herrick, Emmel[3] described the trait in the father of a patient with sickle cell anemia. Since the original descriptions, clinical observations have called attention to the protean manifestations of sickle cell anemia and hematological studies have defined the conditions under which changes take place in the red corpuscles. Much has yet to be learned regarding the pathogenesis of the disorder. Attempts to substitute other names such as *drepanocytic anemia* or *meniscocytosis*, have been unsuccessful.

Incidence

Race

The sickling of red corpuscles has been observed almost exclusively in the negro race or in individuals whose blood contains an admixture of negro blood. For many years there were very few reports of sickle cell anemia outside North America, but it is now clear that this can be attributed to failure to look for the condition. Thus when Trowell[4] began performing routine tests for sickling at a hospital in Uganda, Africa, he found 40 cases of sickle cell anemia per year, whereas previously, between the years 1930 and 1939, none had been seen and only 2 to 5 per year were found between 1940 and 1943. Sickling has now been observed in West and in East Africa. A study in West African soldiers revealed an incidence of sickling of 18.75 per cent in 362 men coming from Nigeria and the Cameroons, 16.6 per cent in 132 natives of the Gold Coast and 28.3 per cent in the men from Gambia. In East Africa[6] an incidence of the trait of 20 per cent was recorded but few had sickle cell anemia.

Trowell[4] has observed sickle cell anemia in members of many tribes of the Bantu race, a group of people speaking allied languages and living in Africa in most districts south of a line which runs almost east to west a little north of the equator. No reports on sickling have been made in the Hamitic race who inhabit Abyssinia and territories to the north, south and east, but whether or not any investigation has been carried out is not clear. No observations appear to have been published on sickling in the Bushman, Hottentot and Negrito (pygmy) races.

Since slaves were recruited to the New World largely from the true negro race and from the Bantu speaking race it would appear that the sickle cell trait was brought to the United States from Africa Search for the trait in other parts of the world has revealed its presence where admixture with negro blood is known to have occurred or was very likely In black Carib Indians in Honduras Central America sickling was found in 8 per cent of a group of 300 In native villages of the Republic of Panama the incidence of the trait was 6 5 per cent[9] In 1 595 inhabitants of the Panama Canal Zone the incidence was 9 6 per cent[8] In another series on the Isthmus of Panama there was an incidence of 14 3 per cent among -64 negroes 1 per cent among 106 mulattos 1 3 per cent among 395 mestizos and none among 105 white persons An incidence of 9 6 per cent has been reported in British West Indians[8] Sickling has been observed in Mexicans[1] [11] An incidence of 10.4 per cent has been reported among negroids in Brazil[1] whereas no instance of sickling was found among 1 545 pure Brazilian Indians[1] Cases of the trait or sickle cell anemia have now been reported in the Argentine[14] and from Peru[1]

The sickle cell trait was found in 7 3 per cent of a series of 8 453 negroes[16] in North America The incidence of the trait among healthy negroes in the United States varies to some extent a higher incidence having been recorded in Memphis Augusta and Detroit and a lower incidence in New Orleans and Baltimore[1] The ratio of the number of cases of sickle cell trait to cases of active sickle cell anemia has been estimated as anywhere from 40 1[16] to 7 1[18] and thus there may be from 000 to 130 000 cases of sickle cell anemia in American negroes

There are now at least 11 reported instances of sickle cell anemia in white families[1] [19] [1] [3] [4] [46] It is of interest that 10 of these were persons of Greek Italian or Sicilian stock Since southern European countries have received African slaves as servants from time immemorial one cannot help but suspect that miscegenation is the explanation for these instances of sickling in apparently pure whites In other reported cases[15] [7] [48] [49] admixture with negro blood was not ruled out satisfactorily

Age and Sex

The *sickle cell trait* has been observed at all ages from birth to old age The incidence of *sickle cell anemia* is highest among children Few cases are observed over the age of 30 probably because of the high

mortality among those affected There is a record of but 6 cases of sickle cell anemia before 6 months of age and only 6 more in the succeeding age period of 6 months to 1 year[30] Watson and associates[30], in studying sickling in 452 consecutive negro newborns and their mothers found that 8 per cent of the mothers and 8 4 per cent of the infants showed the trait It was found that 84 to 100 per cent of the red cells of the mothers sickled, while only 0 5 to 25 9 per cent of those of the newborns took this form Furthermore, the red cells of the latter required a longer time to attain maximum sickling In one instance of sicklemia followed from birth sickling was observed to increase progressively from 6 per cent at birth to 90 per cent at four and a half months of age These differences are attributed to a difference between fetal and adult hemoglobin It is suggested that fetal hemoglobin protects the fetus in utero from sickle cell anemia and is responsible for the slow sickling and lower incidence in the first few months of life, since fetal hemoglobin does not disappear from the blood until 4½ months of age

Although it is generally stated that there is no sex predisposition in two studies in Panama a somewhat higher incidence of sickling in females was observed[8, 9]

Inheritance

The available facts do not give conclusive support to the usually expressed view[31] that a single completely penetrant dominant factor is responsible for sicklemia Thus Neel[32] noted that in 7 of 32 families in which there seemed to be adequate studies, sickling was absent in both parents While impaternity and mutation are possibilities that can be invoked to explain a certain number of apparent exceptions he points out that it is also possible (1) that there may be at least two distinct types of sickle cell anemia one due to a recessive factor and one due to a dominant factor or (2) that the gene responsible for sickling is not always completely dominant and sometimes fails to find any expression at all More female than male parents showed sicklemia in these families in a proportion that corresponded to the different incidence of sicklemia in the two sexes in one large series[8] There may therefore, exist important modifying influences Neel has suggested that there is present in the colored population a certain factor which when heterozygous may have no discernible effects but usually results in sickling and when homozygous tends to result in sickle cell anemia

Evidence has been presented[33] to indicate a linkage between the genes for sickle cells and for the MN blood types

Relation of Sickle Cell Anemia and the Sickle Cell Trait

Some writers have expressed the view that the distinction between sickle cell anemia and the sickle cell trait is an arbitrary one and that cases can be encountered which range between the two extremes of continuous hemolytic anemia and complete good health It has been claimed that in the course of the disease sickle cell anemia the hemolytic process may disappear for a time leaving the picture only of the trait[34] It has been stated[4] that subjects with the sickle cell trait are not always free of symptoms and that some who have a normal blood count have attacks of slight fever and rheumatic pains On the other hand Diggs and associates[16] found children harboring the trait no more anemic than a control group of normal children Unfortunately no really adequate long term observations have been made Most observers consider the sickle cell trait harmless except that it can be transmitted to the offspring This view is supported by the observation[3] that the survival rate of trait cells transfused to normal individuals or to those with sickle cell anemia is like that of normal corpuscles whereas the survival rate of cells from cases of sickle cell anemia is abnormally short

SYMPTOMATOLOGY

In the quiescent state individuals affected with sickle cell anemia show a remarkable adaptation to their state of chronic anemia and jaundice Frequently there may be no complaint of fatigue even though the anemia is severe Others suffer from dyspnea palpitation or weakness In addition from time to time certain symptoms appear and spontaneously disappear which if the patient comes to the physician because of his ailment are usually the presenting complaints They include muscular and arthritic pains sometimes quite severe abdominal pain in some instances extreme fever or chronic leg ulcers

Attacks of pain in the extremities are rarely associated with tenderness swelling or redness of joints although there may be tenderness on pressure over the bones Nevertheless these symptoms are often mistaken for those of rheumatic fever especially since fever of low grade

and even night sweats are common in sickle cell anemia, epistaxis may occur and examination of the heart may yield signs[3] which may be interpreted in the same way The precordium often is overactive Pulsations may be prominent in the neck Sinus arrhythmia is frequent The tachycardia as well as the readily visible, diffuse wavy impulse are accentuated by the thin chest wall The point of maximal apex impulse is not well localized but it is forceful and rolling in character A diastolic tap may be felt in the pulmonic area, and a systolic thrill may be perceptible over the precordium The heart often is enlarged both to the right and left and frequently enlargement is made out in the region of the pulmonary conus A globular shape is commonly noted in the roentgenogram A systolic murmur of variable intensity usually is heard which is maximal early in systole and may be loud enough to obscure the first heart sound Instead a presystolic murmur may blend with the first sound The second sound may be accentuated The murmurs have often been mistaken for those of mitral regurgitation or stenosis or congenital heart disease Electrocardiograms may show sinus arrhythmia, extrasystoles or prolongation of the PR interval Interestingly enough true rheumatic carditis appears to be extremely rare in patients with sickle cell anemia[3]

The abdominal pain may be general but more frequently it is localized in the epigastrium and left hypochondrium and occurs in attacks which often are ushered in by nausea With the abdominal pain there may be generalized abdominal tenderness When this pain is in the right lower quadrant or right hypochondrium acute appendicitis or gall bladder disease may be simulated Prostration and abdominal tension may be associated with sharp, stabbing pain and vomiting and thus the picture may resemble that of other abdominal emergencies and lead to unnecessary operation[38]

In cases of severe sickle cell anemia of long standing the physical appearance often is characteristic[39] The patients usually are underweight, the trunk is short the extremities long and the habitus linear with comparatively narrow hips and shoulders The hands and feet may be long and narrow There may be an increased upper dorsal kyphosis and lumbar lordosis and the chest may be increased in anterior posterior diameter a finding often present even in children In the latter a large abdomen and a small circumference of the legs may attract notice The skull may be tower-shaped as in congenital hemolytic jaundice and there may be saber shins The external genitalia may be atrophic and the facial hair may be scanty



Fig. 1 Sickled erythrocytes.

The palms of the hands and the mucous membranes are pale and the sclerae greenish yellow in color There may be some general lymph node enlargement but palpable splenomegaly occurs only in a small proportion of cases perhaps 15 to 20 per cent[40] The liver may be enlarged The chronic leg ulcers usually are found over the internal or external malleoli They are punched out in appearance single or multiple and unilateral or bilateral They are more common in adolescents and adults than in children

Striking *roentgenographic changes* may be observed in the bones especially in the skull vertebrae tibiae and fibulae[1 41] These are found more frequently in adolescents and adults than in children The skull may at first show a ground glass appearance In more advanced stages a peculiar radial striation is seen A hair-on end appearance is produced by trabecular striations which radiate outward perpendicular to the inner table In later stages the diploe may be thickened the outer table may be poorly defined or there may be osteoporosis In the long bones osteosclerosis with cortical thickening new bone formation within the medullary cavity and patchy irregularities in the density and pattern of the bone structure have been observed

Neurological manifestations are frequent and symptoms such as drowsiness stupor or coma hemiplegia aphasia headache convulsions stiffness of the neck irritability nystagmus pupillary changes blindness (temporary or permanent) cranial nerve palsies and paresthesias of the extremities have been encountered Lesions in the central nervous system generally are multiple and are variable in location The cerebrospinal fluid often is normal but there may be increased pressure sickled erythrocytes xanthochromia and an increase in protein and cells

The veins of the retina may be dilated and tortuous to an extreme degree[4]

Blood Picture

The characteristic feature is the presence of sickle cells (Figure 1) In stained smears most of the red cells are round or oval but they vary in size and macrocytes as well as tiny microcytes may be found A few are elongated and narrow with rounded or pointed ends Other irregularities in shape are unusual Hypochromia is not common but corpuscles with a central dark zone surrounded by a colorless and then a pigmented zone resembling targets are observed frequently The characteristic abnormality of the red cells is brought out by making

a fresh blood preparation When a drop of blood is sealed under a cover slip on a slide or in test tubes[43], a few bizarre multipointed forms may be seen immediately, but changes occur at a maximal rate in from 2 to 6 hours after the blood is drawn First there is thickening of the corpuscle on one side with corresponding thinning on the opposite side The diameter of the corpuscle then becomes greater, and a series of transformations take place rather suddenly which result in the formation of structures of which the most striking characteristics are their tenuous crescentic form and long protoplasmic processes If sickling is marked such changes can be observed also in the counting chamber if the diluted blood is left there for an hour or more The sickling may be made to take place more rapidly by adding a reducing agent to the blood[44] a drop of 2 per cent sodium bisulfite Na S O, a saturated solution of hydrogen sulfide cysteine (0 5 molar solution) or BAL (0 1 molar solution of 2 3-dimercaptopropanol)[4]

The anemia has the features of a hemolytic anemia It may be only moderate in degree (2 5 to 3 million red corpuscles per cubic millimeter) but usually is well marked (2 0 million or less) The reduction in hemoglobin and in volume of packed red cells may be proportionate, so that normal values for mean corpuscular volume and hemoglobin content are found or especially if the anemia is severe and accompanied by marked reticulocytosis it may be macrocytic Nucleated red cells (normoblasts) usually are present ordinarily one to 10 per 100 leukocytes sometimes as many as 40 In addition, there is polychromatophilia and basophilic stippling and Howell-Jolly bodies are not uncommon Nucleated sickle cells are encountered occasionally[40] Reticulocytes may number from 5 to 25 per cent These are usually round or oval and rarely assume the bizarre forms of the non reticulated corpuscles although they are capable of assuming the sickled form[46]

At the same time there is hyperbilirubinemia and increased urobilinuria of varying degree The van den Bergh reaction is indirect as a rule

The resistance of the red corpuscles to hypotonic saline solutions is increased moderately and sometimes extremely, some of the red corpuscles failing to hemolyze even in distilled water The resistance to mechanical trauma is decreased[1, 48]

Leukocytosis is regularly found in sickle cell anemia and when there is active blood destruction, it may be marked (10 000 to 30 000 or more leukocytes per cubic millimeter) There may be a shift to the left and a moderate number of myelocytes At other times the leukocytes

may consist chiefly of multisegmented neutrophils and few young neutrophils or myelocytes Eosinophilia is not infrequent and the monocytes may be increased in number Occasionally red corpuscles may be found engulfed by the latter cells[31]

The platelets often are increased in number also and bizarre forms may be observed Bleeding time and coagulation time usually are normal

The sedimentation rate of the red corpuscles usually is slow even though the anemia is severe[49] This is probably because the abnormal shape of the sickled cells prevents rouleaux formation This has been made the basis of a test which has been found positive only in sickle cell anemia[50] In this test the rate of sedimentation of blood collected from a vein after venous stasis of 6 minutes' duration has been produced is compared with that of the same sample after it has been thoroughly aerated Within 15 to 60 minutes the difference between the sedimentation rate of the sickled venous sample and that of the aerated non sickled cells will be greater than 20 millimeters

Bone Marrow —The findings are those characteristic of hemolytic anemia The greater proportion of the cells are nucleated red cells chiefly polychromatophilic and orthochromic normoblasts which may make up 50 to 70 per cent of all the nucleated cells Megaloblasts such as are seen in pernicious anemia are absent There may or may not be a moderate shift to the left in the myeloid leukocytes and eosinophils may be relatively numerous Megakaryocytes may be present in increased numbers

The Blood in Persons Having Only the Sickle Cell Trait —In those who have only the sickle cell trait there is no anemia and there are no changes in the leukocytes or platelets The red corpuscles in stained smears and in freshly made preparations look normal If however, thin evenly spread cover slip preparations are sealed with petrolatum and allowed to stand at room or incubator temperature a varying number of the erythrocytes will be found to undergo the series of changes already described These changes may not be clearly demonstrable before six or more hours have elapsed They increase up to about 24 hours when frequently the cells return to a circular shape once more The percentage of cells undergoing the changes is very variable in different specimens of blood and in the same blood on different occasions Methods whereby the process of sickling may be speeded up have been discussed already

Diagnosis

The manifestations of sickle cell anemia are so varied that the disease is easily missed if it is not specifically looked for The symptoms may suggest rheumatic fever, osteomyelitis, some abdominal emergency or a neurological disorder The symptomatology of these conditions, in particular, should, in a negro, lead to careful examination of the sclerae for icterus the mucous membranes for pallor and the blood for sickling As distinguished from rheumatic fever, the pain in sickle cell anemia is not limited to the joints but is referred to the bones as well and the characteristic therapeutic response to salicylates does not take place When the manifestations suggest abdominal disease, differential diagnosis is indeed difficult for there may be muscle spasm, leukocytosis vomiting, constipation or diarrhea Even with the full knowledge that one is dealing with a case of sickle cell anemia, exploratory laparotomy may need to be done since the danger from a ruptured ulcer or appendix is greater than the trauma produced by unnecessary operation Generally however a conservative attitude in the face of these complaints is advisable

It is important to avoid confusion where the patient has only the sickle cell trait In such instances hemolytic anemia is absent, and abdominal symptoms related to the sickling do not occur

Treatment

There is no satisfactory form of therapy Sedatives must be given for pain but often they are of comparatively small value In general it is assumed that any measure which decreases circulatory stasis may be helpful Cool baths or douches with the object of dilating the blood vessels of the internal organs by constriction of the peripheral vessels and hot enemas have been recommended for the treatment of abdominal pain[34] If there is an abdominal crisis, plasma or whole blood transfusions may be helpful for the condition of the patient may border on shock Insofar as relief from anemia is concerned, blood transfusions are of but temporary value Liver or iron therapy is useless Splenectomy has been reported as valuable when there has been marked splenomegaly When the spleen is small splenectomy is of no help Prolonged rest and mecholyl iontophoresis have been beneficial in the treatment of chronic leg ulcers in some instances

Course Complications and Prognosis

Sickle cell anemia is a disease of remissions and relapses The relapses may persist for weeks or months and may be followed by months or even years of few symptoms There is no good evidence however that the anemia disappears entirely or that the evidences of blood destruction ever are relieved completely The factors, which influence remission and relapse are unknown

The ultimate outcome is fatal Most patients die in the first decade of life Very few survive beyond the third Death may occur from intercurrent infections especially tuberculosis from cardiac failure as the result of thrombosis or hemorrhage involving vital tissues of extreme anemia in association with an abdominal crisis or in uremia after the development of marked renal impairment

Gall stones may form and cause symptoms Abortion is likely if conception occurs at all but pregnancy has occurred and had been carried to a successful conclusion in a few instances [1]

Pathology

The essential findings at autopsy are the evidences of hemolytic anemia and the effects of circulatory disturbances Siderofibrosis is found in the spleen and hemosiderosis in the liver kidneys lymph nodes and bone marrow The bone marrow of the flat and cancellous bones of the trunk the calvarium and the long bones of the extremities shows hyperplasia The smaller bones of the hands and feet however may contain only fat[11] The marrow is soft and jelly like uniformly dark red or purplish black The microscopic appearance has been described already There may be abnormal calcification and new bone formation

In the inner organs many large foci of ischemic necrosis may be found Although reference has been made frequently to the presence of thrombi a critical analysis reveals that these are relatively uncommon and that degenerative changes in the vessel walls are rare Capillary thromboses may occur and capillary stasis is commonly noted Ischemic infarctions have been described more often in the absence of than together with related thrombi

The spleen shows thickening of the capsule and trabeculae and there is a great increase in reticulum The vascular alterations are similar to those described in other tissues The sinuses are greatly engorged

with blood which produces pressure upon distortion and finally atrophy of the Malpighian bodies The capillaries of the Malpighian bodies are often so dilated that they present the appearance of multiple varices Infarction is common Eventually fibrosis and shrinkage of the spleen occur, and in the last stages the spleen is reduced to a tiny wrinkled mass weighing as little as 16 grams The pooling of the blood in the red pulp cords of the marginal zones is probably attributable to the presence of clumps of sickled cells rather than to a congenital defect [3]

The kidneys may be smaller than normal and irregular in contour with slight thinning of the cortex and brownish pigmentation of the medullary portion In the brain dilatation of peripheral blood vessels and congestion with sickled erythrocytes as well as necrosis and in some instances multiple thromboses have been observed

It is noteworthy that formalin although a reducing agent fixes red cells in whichever form they are exposed to it, whether sickled or not[44] Zenker s fluid however, causes already sickled corpuscles to reassume a discoidal appearance

Pathogenesis

It has been clearly demonstrated that sickling is a property of the red cells rather than of the plasma[31] Assumption of the crescentic shape occurs in an atmosphere deprived of oxygen and is favored by a lowering of the pH[43, 54] Exposure to oxygen or carbon monoxide is effective in restoring sickle cells to a circular form[54] High temperature favors sickling Low temperatures tend to inhibit it[43] The number of leukocytes or bacteria is a contributing factor probably because of their influence on the oxygen content of the sealed preparation It is of interest that erythrocytes capable of assuming sickle shapes will do so when resuspended in normal saline but multiple washings have been reported to remove some substance from the cells themselves which is necessary for the phenomenon of sickling[5] It has been suggested that this is carbonic anhydrase A curious observation[56], awaiting interpretation, is the demonstration that in marked contrast to the blood of normal subjects or of patients with anemia of various types including hemolytic anemias and even in contrast to the blood of subjects with the sickle cell trait the red cells of sickle cell anemia are capable of synthesizing heme from glycine in vitro

Sickling has not been observed directly in circulating blood but higher proportions of sickled cells have been found in venous blood collected under oil than in similar specimens of arterial blood[12] Furthermore it was found[7] that when patients with sickle cell anemia were allowed 70 to 100 per cent oxygen the percentage of abnormal forms was less in both arterial and venous blood than during pre and post oxygen periods Curiously enough no consistent detectable change in rate of hemolysis occurred during 8 to 20 day periods of oxygen administration Both the percentage of reticulocytes and the number of red cells decreased during the periods of oxygen administration After the latter was discontinued a striking reticulocytosis developed and the erythrocyte count rose to the pre oxygen levels These studies have been corroborated by observations on the effect of lowered oxygen tension on military flying personnel with the sickling trait and in a subject with active sickle cell anemia[8]

The cause of the hemolysis in sickle cell anemia is obscure In hypotonic saline solutions sickle cells are more resistant to destruction than are normal corpuscles On the other hand as already mentioned their mechanical fragility is greater than normal There is no evidence to support the suggestion[31] that the blood destruction seen in cases of sickle cell anemia is produced by mechanical impaction of masses of deformed red cells in the smaller blood vessels of various organs It has been found[7] that cells from a normal individual introduced by blood transfusion to a patient with sickle cell anemia while in crisis disappear at a normal rate even though the patient's own red cells are being destroyed rapidly On the other hand as already indicated cells from a person with sickle cell anemia when transfused into trait carriers have a shortened life span about one fourth of the normal[25]

The sickling process thus may be the expression of an abnormality of the stroma but the pathogenesis of the anemia is obscure Experimental studies[7] give no support to the assumption that anoxemia initiates a train of events consisting of corpuscular distortion vascular stasis and thrombosis It has been suggested[3] that sickle cell anemia develops because of an additional alteration in the cyto-skeleton which is quantitatively different from the structural anomaly responsible for the sickling phenomenon Possibly alterations of the stroma which occur with aging when superimposed on an already structurally defective cell may lead to massive disintegration of erythrocytes in a short period of time This is followed by the production and release of many young cells from the bone marrow which being of the same age disintegrate

at the same time, the process thus repeating itself in accordance with the average survival time of the cells in the circulation

The clinical picture of patients with the abdominal crisis of sickle cell anemia is similar to that of shock, and this has been attributed[60] to the packing of sickled erythrocytes in small capillaries thus removing them from a functional status and adding to the anemia already present The capillary anoxemia results in plasma loss hemoconcentration and further stagnation The factors which initiate such episodes are no clear but histological studies indicate that they may be accompanied by vascular spasms which increase tissue anoxia and lead to ischemic necrosis in inner organs or to capillary dilatation or stasis It has been suggested that engorgement of capillaries and their packing with sickle cells may be the result rather than the cause of capillary stasis A further consequence may be organic damage to vessel walls degenerative changes thrombosis and infarctions

The pathogenesis of the cardiac manifestations may be related to impaired circulation in the lungs as the consequence of the circulatory derangement, just described with cor pulmonale resulting[61] It is also possible that the sickle cell heart represents in extreme degree the consequence of cardiovascular adjustments to an anemia which unlike other forms of anemia to which the cardiovascular and respiratory apparatus must adjust itself is continuously severe for a great number of years[6]

The pathological alterations in the bones can be accounted for by hyperplasia compensatory to the increased blood destruction with osteosclerosis developing as a secondary phenomenon Whether skeletal malformations and the signs of endocrine deficiency represent the effects of sickling or are like sickling manifestations of a degenerative stigma[31] is not clear

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CHAPTER XXIV

METHEMOGLOBINEMIA AND SULPHEMOGLOBINEMIA AS RELATED TO ENTEROGENOUS CYANOSIS

By GEORGE A HARROP JR

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Definition — Methemoglobinemia and sulphemoglobinemia are conditions due to the presence in the blood of the abnormal pigment methemoglobin and sulphemoglobin respectively. They are associated with a peculiar coloration or "cyanosis" of the skin and mucous membranes, i e accompanied frequently by gastro-intestinal, neurologic or psychic disturbances and less commonly by disorders of the special senses. Blood changes may occur as a result of the presence of the abnormal pigment directly, or much more commonly they may accompany the condition as an additional consequence of the action of the causative agent. Abnormalities of the circulation or cardio respiratory system so common in other types of cyanosis are conspicuously absent or have no direct relation to the cyanosis produced by methemoglobin or sulphemoglobin. Methemoglobinemia has also been called "false cyanosis." Hijmans van den Bergh has suggested the term *parhemoglobinemia* as an inclusive title for all such disorders of hemoglobin function. Although excellent, this suggestion as yet has not been adopted widely.

The term *enterogenous cyanosis* embraces a special group in which one or both of these abnormal pigments may be present, but in which the known action of specific causative poisons seems to be definitely ruled out. The condition in such cases usually has been attributed to the action of compounds

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the use of nitrites and of nitro glycerine Among the important factors is the size of dose the period of administration and the occurrence of gastro intestinal disorders Methemoglobinemia also may occur in nitric acid poisoning due it is believed to the formation of nitrites

The important group of poisons which produce methemoglobinemia is that composed of aniline and its derivatives These produce their effects either by contact in industry or by the overuse of coal tar medicaments Among the latter, phenacetin and acetanilid (antifebrin) and the various patent preparations in which they occur are of greatest importance because of their widespread use Symptoms of intoxication other than those due to the abnormal blood pigment formation are associated frequently The transformation to paramidophenol in the body is said to be a necessary intermediate step in methemoglobin formation with these compounds Among the more important members of the group used in industry from the point of view of this type of poisoning is mononitrobenzene (oil of mirbane) used in the dye industry and (in France) in the manufacture of perfumes and confections This compound passes rapidly through the skin surfaces and even when spilled or splashed after a comparatively slight accident may give rise to severe intoxication When the clothing is soaked collapse may occur at once but characteristically symptoms are delayed owing it is said to the relative insolubility of the compound in water The toxic symptoms from amido derivatives (NH) of the benzene ring are less serious than the nitroso (NO) or nitro (NO) compounds in which however more extensive methemoglobin formation and hence deeper cyanosis occurs Of special recent intere t is the use of aniline in the rubber industry as an accelerator of the process of vulcanization (hardening by compounding with sulphur) Many chronic cases were reported from Akron Ohio where the victims called blue boys were seen frequently in the early days of the war period Other industries where the use of aniline compounds cause trouble are the leather and harness trades and from contact with shoe polish Steady progress is being made in the prevention of these cases by the intelligent use of protective devices where exposure is necessary At the present time the most serious danger probably occurs in various phases of the dye and color industries

It is extremely difficult to separate the clinical effects due to methemoglobinemia alone from the other effects due to the particular poisoning agent implicated and this no doubt accounts for the reported variation in symptomatology There is no definite evidence that methemoglobin per se has any effects on the body other than those due to anoxemia Characteristic is the rapid removal of the pigment from the blood as soon as the causative agent can be found and removed with rapid clearing up of the cyanosis The blood hemoglobin pigment may contain as much as ixty per cent in the form of methemoglobin it

abnormal either in kind or in amount which are produced in the gastro-intestinal tract

Incidence

Sex and age seem to play no definite role in etiology Both methemoglobinemia and sulphemoglobinemia (enterogenous) have been reported repeatedly in young children and even in infants Davis believes that blonds are more susceptible to poisoning with aniline dyes than are brunettes, that young people are affected more readily than those of middle age and that alcoholism tends to increase susceptibility to the production of methemoglobinemia by these compounds

The investigation of methemoglobin and sulphemoglobin is associated particularly with the development of the aniline dye industry during the latter part of the nineteenth century It is to Hoppe Seyler that we owe the identification and original investigation in 1863–64, of both methemoglobin and sulphemoglobin the methods of their formation and their properties in relation to the parent substance, hemoglobin During the following decades a considerable body of knowledge was acquired regarding the clinical features of methemoglobinemia although the chemistry of methemoglobin thanks particularly in this country to the studies of Conant, has become well understood only within the past few years

Methemoglobinemia

Methemoglobin is readily formed from ordinary hemoglobin simply by allowing laked blood to stand or more readily by the addition of a considerable variety of reagents of differing chemical properties These in turn sometimes have differences of effect depending on whether the action takes place in vitro or in vivo For example methemoglobin may be formed by the addition of either oxidizing or of reducing agents of certain types and although potassium ferricyanide readily produces this pigment in vitro (this reaction is at the basis of the present standard methods of blood gas analysis for oxygen), it appears to have little or no effect in forming methemoglobin when injected into the animal body

Of clinical interest in the production of methemoglobinemia, among the various oxidizing agents is poisoning with the chlorates of sodium ammonium and potassium, all of which are used in the manufacture of Swedish matches fireworks and explosives The latter salt has been used extensively as a gargle A single dose of 30 g is fatal although not necessarily so if the dose is divided Idiosyncrasies to the drug exist Medicinal poisoning occasionally occurs from

contrast is observed especially well in drawn blood, or if a comparison is made between test tubes filled with laked blood containing methemoglobin and sulphemoglobin respectively These may be readily prepared by addition of a few drops of dilute potassium ferricyanide solution to the one while the addition of a small amount of sulphuretted hydrogen water will yield the other The cyanosis which is due to sulphemoglobin tends to be most marked in the lips nail beds and mucous membranes of the mouth less commonly about the nose and ears In contrast to the color changes produced by methemoglobin it is strikingly absent from the skin in general which in severe cases may exhibit a waxy like pallor (*b*) A history of chronic constipation is very common (*c*) *Habitual and extreme headaches were present in all but two of our patients* These often commence in youth and increase in severity through life (*d*) A record of the chronic use of drugs and particularly of aniline derivatives for the relief of headache is very common Especially to be mentioned is the use of acetanilid particularly in our experience in the form of bromoseltzer, which is said to be a compound containing acetanilid potassium bromide and caffeine (*e*) Emotional instability is encountered frequently probably a consequence of drug addiction in chronic cases or associated with the constipation and severe headaches The tendency of sulphemoglobinemia to appear following the prolonged use of phenacetin was noted by Snapper (19 2) who considered that the drug in some way sensitized the hemoglobin so that it was readily converted into sulphemoglobin by the small amounts of hydrogen sulphide which may diffuse into the blood in the intestinal area and which are normally ineffective Snapper s explanation possibly holds for the effect of the chronic use of acetanilid (antifebrin) and other similar drugs as well

Both Hijmans van den Bergh and Snapper draw attention to the fact that sulphemoglobinemia is produced more readily in persons suffering from liver disease (especially cirrhosis) and we have ourselves observed that the mere feeding of flowers of sulphur in amounts insufficient to cause diarrhea quite regularly and easily produces sulphemoglobinemia in splenectomized dogs Sufficient data has not been accumulated yet to indicate whether the same thing holds true for man

The exact relationship of sulphemoglobin to normal hemoglobin is not yet clear It has been suggested but not proved that it is a compound analogous to methemoglobin with substitution of sulphur in place of oxygen It cannot be reconverted into hemoglobin as can methemoglobin and it is in general quite stable This offers an adequate explanation for the fact that sulphemoglobin remains for long periods unaltered in the blood without either elimination or reconversion, and that the cyanosis may be obvious in the patient for long periods after the removal of any possible offending etiological agent Evidence which appears to be good indicates that sulphemoglobin is formed from reduced

is said, without necessarily resulting in a fatal termination Due to the rapid disappearance of the pigment, doubtless in most instances due to reconversion into normal hemoglobin, polycythemia usually does not result from the stimulus of anoxemia On the other hand, anemia may occur where extracellular methemoglobin is formed and excreted in the urine In most cases, however, anemia must be looked upon as a further effect of the intoxicating agent and not as a direct result of methemoglobinemia

Clinical Features

The color change in the skin and mucous membranes generally is proportional to the amount of methemoglobin in the circulating blood Doubtless considerable modification may be due to pigmentation in the skin itself The dark color of the blood in the retinal vessels may be observed on ophthalmoscopic examination The color in methemoglobinemia is bluish brown and appears over all the skin surfaces and mucous membranes and is prominent in the nail beds The occurrence of deep cyanosis' of this character, unaccompanied by evidences of lung or cardiac disease, should arouse strong suspicion of this condition especially with a history of prolonged use of drugs Constipation is not characteristic in some of the cases of enterogenous cyanosis due to methemoglobin reported by the Dutch observers diarrhea was a striking finding Clubbing of the fingers is uncommon but has been described in cases of very long standing Headache, visual disturbances and tinnitus have been described Mental dullness and irrational behavior, slurring of speech and lack *of cooperation may be due to the effects of anoxemia In all cases* toxic effects of the drug responsible, or of other drugs may produce symptoms apart from and not directly due to the methemoglobinemia

Sulphemoglobinemia

Sulphemoglobinemia was first noted as a clinical entity by Hijmans van den Bergh in 1902 and for many years has been considered an extremely rare condition only about thirty cases having been reported up to 1930, of which but five have been described in the United States We have, however, observed fourteen cases at the Johns Hopkins Hospital, alone, during the past four years It is evident that many cases escape observation and that frequent confusion probably exists in the differentiation between methemoglobinemia and sulphemoglobinemia Certain clinical features especially characterize the latter condition These are — (*a*) Character of the cyanosis, which tends to be of a mauve or lavender tinted blue whereas in methemoglobinemia the blue element of the skin coloration tends to be mixed with brown or chocolate shades The

plus abnormal) hemoglobin in several of our cases of sulphemoglobinemia In general the ogygen capacity was very little reduced in fact in most of the cases it was normal or even above normal The amount of sulphemoglobin present at the same time in these cases of moderate severity varied between 3 and 5 per cent by volume reckoned in equivalents of oxygen capacity of hemoglobin This means that the total hemoglobin, the sulphemoglobin and oxyhemoglobin together was greatly in excess of the normal total pigment It would thus appear that in individuals who are chronic drug addicts and are continually converting part of their hemoglobin into the non oxygen carrying pigment sulphemoglobin there occurs a compensatory overproduction of blood pigment

Enterogenous Cyanosis

Enterogenous cyanosis is a term which has been used to designate occurrence of methemoglobin or of sulphemoglobin in the circulating blood where an obvious cause cannot be found The abnormal pigment may occur either within the erythrocytes (intra corpuscular) or dissolved in the serum The term ' enterogenous implies that it is produced by reason of some pathological condition in the intestine quite apart from the employment of any drug or external toxic agent The first such case was described by Stokvis in a man of 38 who suffered from a severe enteritis associated with marked cyanosis of kin and mucous membranes and clubbing of the fingers Spectroscopic study revealed methemoglobin Talma shortly after reported three cases with the same symptom complex marked cyanosis of skin and mucous surfaces clubbed fingers severe enteritis and methemoglobin in the blood which was present only in the cells Both authors considered the condition to be a result of auto-intoxication from materials produced in the gut Hijmans van den Bergh reported two cases of enterogenous cyanosis one a boy with congenital anal stenosis and sulphemoglobinemia the first reported case The second was one of methemoglobinemia and was noteworthy in that it was greatly improved when the patient was on a milk diet The cyanosis grew rapidly worse again on mixed diet and was most severe when quantities of meat were eaten

Most cases of sulphemoglobinemia are classified also as examples of enterogenous cyanosis but we have reported recently one due to exposure to aniline dyes and hydrogen sulphide The occurrence of both pigments simultaneously or of one succeeding or alternating with the other is not infrequent From time to time reports have been made of the presence in the blood of other hemoglobin derivatives distinguishable by spectroscopic means or otherwise as after poisoning with nitro-compounds or spontaneously following splenectomy These lack definite characterization at the present time and so far certainly are of negligible clinical significance

hemoglobin, but that oxygen is necessary to its formation from reduced hemoglobin and very probably enters into the formation of the sulphemoglobin molecule Another interesting distinction from methemoglobin is the relative slowness, judging from the changes in the spectrum bands, of its formation in vitro after the addition of the sulphide

Spectroscopic Tests

In all but the mildest grades of cyanosis the presence of one or other of the abnormal pigments may be demonstrated with a pocket spectroscope by examining a bright light shining through the ear or the cheek of the patient In milder cases and when it is desired to distinguish between the two pigments by differential tests, blood is drawn from the finger into a tube of water, or from a vein into a tube containing oxalate The blood is then diluted in the tube until one can just see a bright light through it Normal blood examined in this way cuts out the whole of the spectrum except the orange and red region, which appears as an unbroken strip of color In blood containing either methemoglobin or sulphemoglobin a dark absorption band is seen cutting the colored strip in two, orange on one side, red on the other The methemoglobin band is nearly in the middle of the strip the sulphemoglobin band is more toward the blue side of the middle, so that it makes the orange strip on one side of it narrower than the red strip on the other side

The pigments can be distinguished more definitely by certain tests

1 If a drop of dilute ammonium sulphide or of 1 per cent potassium cyanide is added to the blood, the methemoglobin band immediately disappears the sulphemoglobin band is unchanged

2 If carbon monoxide be bubbled through the blood the sulphemoglobin band shifts slightly towards the blue the methemoglobin band does not move

3 With suitable apparatus the wave length of the band can be measured, and the measurements compared with those of the bands given by standard solutions of the two pigments

4 When both pigments are present in the blood, the two bands overlap and appear as a single band Its double origin can be demonstrated easily by dividing the solution between two tubes and adding to one of them a drop of potassium cyanide A simultaneous comparison of the two tubes will show that the band in the second tube has been amputated on its red side

Quantitative Determination of Pigment

Quantitative determinations by a combined gasometric and colorimetric method, were made of the oxyhemoglobin sulphemoglobin and total (normal

plus abnormal) hemoglobin in several of our cases of sulphemoglobinemia In general the oxygen capacity was very little reduced in fact in most of the cases it was normal or even above normal The amount of sulphemoglobin present at the same time in these cases of moderate severity varied between 3 and 5 per cent by volume reckoned in equivalents of oxygen capacity of hemoglobin This means that the total hemoglobin the sulphemoglobin and oxyhemoglobin together was greatly in excess of the normal total pigment It would thus appear that in individuals who are chronic drug addicts and are continually converting part of their hemoglobin into the non-oxygen carrying pigment sulphemoglobin there occurs a compensatory overproduction of blood pigment

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Treatment

The principal therapeutic indication is directed to the removal of the etiological agent, when it can be recognized, and to attention to proper personal hygiene Of especial importance is the efficient relief of constipation, particularly in cases of sulphemoglobinemia Besides the ordinary measures during the acute period, the use of intestinal irrigation and enemata at frequent intervals for a considerable period of time may be advisable A diet high in carbohydrates and low in meat proteins should be employed, especially in cases of methemoglobinemia, in view of the striking results of Hijmans van den Bergh as cited above No other medication is of the slightest value It is the rule for methemoglobin to clear up rapidly from the blood once the offending cause is removed, while the cyanosis due to sulphemoglobin may last for weeks or months

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CHAPTER XXV

FAVISM

By THOMAS McCRAE

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Favism (fabism fabismus) is a syndrome due to inhalation of pollen from the bean plants (*Vicia fava* or *faba*) when in blossom or by ingestion of the beans raw or cooked, and characterized by very severe acute anaemia jaundice haematuria and haemoglobinuria The syndrome occurs most frequently in Sardinia Sicily and southern Italy and the majority of the reports are in the Italian literature An excellent account was given by Gasbarrini Some cases of asthma have been reported as due to the pollen of the bean

History —The condition has been recognized from ancient times and is mentioned in the works of Herodotus Pythagoras and Empedocles The modern study dates from about the middle of the last century In some of the articles written at that time it was recognized that persons who are susceptible might fall in syncope and sometimes die if they came near a field of the plants in bloom The first complete study was by Montano in 1894 and following this a considerable number of articles have been published

Etiology —Geographically the disease seems to be limited almost entirely to certain localities where the Vicia bean is grown It is evident that this applies to the cases due to inhalation of the pollen but there does not seem to be any explanation for the apparent localised occurrence of cases due to ingestion of the beans It would seem that in susceptible persons the condition might occur any

Treatment

The principal therapeutic indication is directed to the removal of the etiological agent, when it can be recognized, and to attention to proper personal hygiene Of especial importance is the efficient relief of constipation, particularly in cases of sulphemoglobinemia Besides the ordinary measures during the acute period, the use of intestinal irrigation and enemata at frequent intervals for a considerable period of time may be advisable A diet high in carbohydrates and low in meat proteins should be employed, especially in cases of methemoglobinemia, in view of the striking results of Hijmans van den Bergh as cited above No other medication is of the slightest value It is the rule for methemoglobin to clear up rapidly from the blood once the offending cause is removed, while the cyanosis due to sulphemoglobin may last for weeks or months

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usual manifestations of anaphylaxis Among other suggestions are the toxic theory the substance being in the bean or in a fungus growing on the bean and the infection theory In favor of the toxic theory are the usual absence of a period of incubation the short duration and the similarity to the picture produced by some vegetable intoxications In favor of the infection theory are the fever and leucocytosis Blood cultures have always been negative The experimental work on animals has not thrown much light on the problem and the results have been very variable Few autopsies have been reported and the findings do not seem to have been striking

Clinical Features —The incubation period is short when the condition follows inhalation from the flowers and may be from one to six hours Usually it is longer following the ingestion of the beans and may be from one to two days In my patient the symptoms came on within an hour after the ingestion of the beans.

In certain instances there is marked prostration and weakness with unconsciousness which may last for some hours or there is headache vertigo twitching of the muscles increased respiration rate nausea and vomiting Some patients show marked gastro intestinal disturbance others have none Chills may occur and fever is usual There is very marked pallor which comes on quickly with the rapid onset of severe jaundice Usually within an hour after the onset large amounts of bile are found in the urine Another striking manifestation is haemoglobinuria and haematuria which come on in a short time and which may disappear rapidly The amount of blood may be quite large and red blood cell and haemoglobin are found in the urine Haemoglobinaemia may be found within a few hours of the onset The anaemia is a very striking feature and there may be such rapid destruction of red blood cells that in some cases the number falls to about 1 000 000 and the haemoglobin to 20 per cent or lower in a short time Some reports state that the red cells had fallen to 1 000 000 in a few hours The red cells show variations in size and staining stippled and immature red blood cells may be found At the onset there may be leucopenia which usually is followed by marked leucocytosis There is an increase in the mononuclear elements but no eosinophilia It is stated that the blood platelets are greatly diminished at the onset and that a later increase is a favorable sign Sometimes the number of platelets is greatly increased The fragility of the red cells does not seem to be increased and auto agglutination has never been found The serum of the patients has no haemolytic action either on the patient s blood or on that of normal persons

The fever is very variable and rarely rises above 103 F In patients who recover it usually does not last for more than four or five days and falls by lysis Repeated severe chills may be a marked feature

The character of the attacks varies greatly from mild abortive forms to acute forms which result in death in 24 or 48 hours The heart usually is rapid and

where from eating the beans, but how often the syndrome occurs in other countries from this cause it is impossible to state. After the publication of our case, letters were received from several physicians giving the accounts of cases in different parts of the United States which strongly suggested favism.

Heredity. — This seems to have a definite influence and in some of the reported series was a factor in about [illegible]0 per cent. of the cases. There are some families in which apparently every member has been susceptible for many generations and it is stated that in these families the disease is apt to be exceedingly severe.

The individual predisposition seems to vary markedly. Some are not susceptible to inhalation from the flowers but develop the condition after eating the beans, the contrary may also be true. Only a small proportion of those who inhale the pollen or eat the beans are affected. The individual predisposition varies greatly from time to time and may appear for a year or two and then disappear. The first attack may occur in adult life or in old age. The accounts suggest a remarkable variation in susceptibility from year to year. It is rare for a patient to have a recurrence in the same year.

Sex and Age. — These seem to have no influence and the disease may occur at any age. The disease has occurred in nursing infants when the mother has eaten the beans.

With regard to the relative importance of inhalation and ingestion in a series of 1211 cases (Fermi 1905) 459 (38 per cent.) were due to inhalation and 725 (62 per cent.) to ingestion of the beans, raw or cooked. Apparently the fresh raw beans if eaten are more likely to cause symptoms than when cooked or dried.

Pathogenesis. — Haemolysis is the most marked phenomenon in the disease or syndrome. There are difficulties in giving a complete explanation of the process, but allergy is strongly suggested. There seems to be no association between the amount of pollen inhaled or the quantity of beans eaten and the severity of the attack. A long exposure to the plants in flower or ingestion of a large amount of beans may be followed by a mild attack. This is evidence against the toxic theory. An anaphylactic reaction has been obtained in animals which have been sensitized to the beans. Animals can be rendered sensitive by feeding the beans or injecting the protein of the bean. The study of Parlato[3] shows that the pollen of the bean might cause both hay fever and asthma and he obtained positive skin reactions. In my patient we were unable to obtain any reaction by intradermal skin tests but subcutaneous injection of larger amounts caused symptoms suggestive of those of the attack. The curious variability and susceptibility in individuals suggest that, if there is sensitivity, it is not constant. The general opinion is that the syndrome represents a hypersensitiveness to the protein of the bean and that the manifestations are due to anaphylaxis. If so, it differs from the

dilatation seems to be fairly common, the increased rate may persist for some time Epigastric pain with nausea and frequent vomiting may occur As a rule there is constipation in adults and diarrhoea seems to be more common in children The liver and spleen usually are enlarged and somewhat tender The enlargement of the spleen usually is relatively more than that of the liver In severe cases toxaemia may be marked with stupor or delirium

There does not seem to be any tendency to relapse or recrudescence As soon as the haemoglobinuria disappears the patient begins to recover Improvement usually begins from the second to the fourth day There does not seem to be immunity to the condition

Diagnosis —This should not be difficult in regions where the disease is common but elsewhere, when due to eating the beans, may be very difficult, especially if the attack is mild The picture, coming on acutely, of fever, severe anaemia, jaundice and haemoglobinuria (perhaps with haematuria) is striking, and the possible causes are not many Malarial haemoglobinuria should be readily distinguished and paroxysmal haemoglobinuria shows a specific autolysis in the blood by the Doneth Landsteiner test which is absent in favism Slight or abortive forms of favism will be difficult to diagnose anywhere

With regard to prognosis, the danger of death seems to be greater in children than in adults The chief danger is from the severe anaemia A study of the mortality in Sardinia showed a death rate of 8 per cent It is pointed out that the severity of the disease seems to vary a great deal in different years

Prevention —Susceptible individuals evidently should avoid the locality of the beans in flower and abstain from eating them in any form One wonders at the repeated exposure to the danger of an attack in those who live in localities where the disease is common Nursing mothers should not be allowed to eat the beans

Treatment —This is symptomatic The patient should be at rest in bed, on liquid diet and given alkalies freely If the symptoms of shock are marked in the early stages epinephrine may be given hypodermically If the anaemia is very severe, blood transfusion is indicated, and this should be repeated if necessary The patient should be nourished as well as possible, and the bowels freely moved if there is constipation In convalescence large doses of iron should be given Attempts to influence the haemoglobinuria apparently have not been successful

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